A PHASE 2B/3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF PF-06651600 IN ADULT AND ADOLESCENT ALOPECIA AREATA (AA) SUBJECTS WITH 50% OR GREATER SCALP HAIR LOSS

Investigational Product Number:	PF-06651600
Investigational Product Name:	Janus Kinase 3 inhibitor
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2018-001714-14
Protocol Number:	B7981015
Phase:	2b/3

Document History

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Amendment 5	13 April 2021	• In the Protocol Summary – Objectives and Endpoints, in Section 2, Objectives and Endpoints, and in Section 9, Data Analysis/Statistical Methods, language was added to clarify the known regional requirements for the analysis of primary and secondary endpoints. Rationale: Differences in regulatory feedback from various regions have necessitated distinctive reporting requirements for the primary and secondary endpoints. These differences were already described in the protocol; this language provides more clarity. • Throughout the protocol, a key secondary objective for the study was added with the key secondary endpoint of "Response based on an absolute SALT Score ≤10 at Week 24". This key secondary endpoint will be analyzed utilizing an appropriate testing procedure to control overall Type I error. This change applies to the overall study; therefore, it does not change the primary and key secondary objectives and endpoints for the European Medicines Agency (EMA), which are different than those for the overall study and remain the same as the one from previous version of the protocol. a key secondary objective for the study was added with the key secondary endpoint of "To evaluate the efficacy of PF-06651600 compared to placebo in adult and adolescent alopecia areata (AA) subjects with 50% or greater scalp hair loss on regrowth of lost hair (as measured by an absolute Severity of Alopecia Tool (SALT) Score ≤10) at Week 24". A secondary endpoint of "Response based on an absolute SALT Score ≤10 at Week 24" was also added and will be analyzed as a key secondary endpoint utilizing an appropriate testing procedure to control overall Type I error. This does not change the primary and key secondary objectives and endpoints for the European Medicines Agency (EMA), which remain the same. Rationale: Previous versions of the protocol indicated that when SALT ≤20 response at Week 24 is utilized as the primary endpoint, SALT ≤10 will be analyzed controlling for Type I error. This change formalizes that analysis in the form of a key secondary endpoint. • Throughout the protocol, the secondary endpoint of "Response based on a SALT score of ≤10 at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48" was updated to clarify that this refers to "an absolute SALT score" for consistency with other SALT endpoints. Rationale: This change has been made to correct a typographic error. • In the Protocol Summary – Objectives and Endpoints and in Section 2, Objectives and Endpoints, clarification was added regarding the key secondary endpoint of "PGI-C response defined as a score of "moderately improved" or "greatly improved" at Week 24" for the EMA and competent authorities in the Voluntary Harmonisation Procedure (VHP) countries. Rationale: This key secondary objective for the EMA and competent authorities in the VHP countries was already described in the protocol; addition of this language in the tables describing the study objectives and endpoints in the Protocol Summary – Objectives and Endpoints and in Section 2, Objectives and Endpoints (rather than just in the footnotes) provides more clarity.

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		• In the protocol summary, the secondary endpoint for the Patient's Global Impression of change (PGI-C) response was updated from "PGI-C response defined as a score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48" to "PGI-C response defined as a PGI-C score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48". Rationale: This change has been made to ensure consistency with the wording of this endpoint in Section 2. • In the Protocol Summary – Statistical Methods and in Section 9.7, Interim Analysis, language was added to provide clarification on the objective of the interim analysis and that the results will have no impact on the study conduct, analysis, or reporting. Rationale: This change has been made at the request of the United States Food and Drug Administration (FDA) to clarify the objectives of the interim analysis. • In the Protocol Summary – Statistical Methods and in Section 9.1, Sample Size Determination, the sample size section was updated to incorporate the power of the study based on the key secondary endpoint of SALT ≤ 10 at Week 24, and using the α levels of 0.01 (for EMA) and 0.00125 (for FDA/Japan Pharmaceuticals and Medical Devices Agency [PMDA]). Rationale: This change has been made to align with the reorganization of the endpoints for the study. • In the Protocol Summary – Statistical Methods and in Section 9.1, Sample Size Determination, a reference was added for the abstract presenting the Concert CTP-543 Phase 2b Study Week 24 data which was used to estimate the treatment difference and placebo response rate for the Patient's Global Impression of Change (PGI-C). Rationale: This change has been made to correct an error of omission. • In the Protocol Summary – Statistical Methods and in Section 9.2, Efficacy Analysis, the definition of the Full Analysis Set (FAS) was updated. Rationale: This change has been made at the request of the FDA to include all subjects, regardless of whether they received study medication, in the FAS. • In the Protocol Summary – Statistical Methods and in Section 9.2.1, Testing Procedure for Multiple Comparisons, this language was revised. The Protocol Summary reflects the testing procedure overall for the study and Section 9.2.1 and new Sections 9.2.1.1, 9.2.1.2, and 9.2.1.3 detail the testing procedures used for the overall study, for the FDA/PMDA, and for the EMA. Rationale: This change has been made to align with the reorganization of the endpoints for the study. • In the Protocol Summary – Statistical Methods and in Section 9.2.2, Analysis of the Primary and Key Secondary Endpoints, this language was revised. The statistical methods for the analysis of the primary endpoint for the EMA were revised. Section 9.2.2, Analysis of the Primary and Key Secondary Endpoints was re-organized by adding new Sections 9.2.2.1 and 9.2.2.2 to detail the analyses used for the overall study, for the FDA/PMDA, and for the EMA. In addition, description of the per-protocol analysis was moved to a separate section (Section 9.2.2.3).

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		Rationale: This change has been made to incorporate advice received from a European national agency regarding the approach for how missing data due to COVID-19 should be handled in the analysis of the primary endpoint. • In the Protocol Summary – Statistical Methods and in Section 9.2.2.1, For the Overall Study, the FDA/PMDA (Analysis of the Primary Endpoint), the procedure for handling of missing data was updated to exclude subjects from the primary analysis who are missing the SALT assessment at Week 24 due to coronavirus disease 19 (COVID-19) related reasons. Subjects with SALT assessments missing at Week 24 for other reasons will be counted as non-responders. In addition, a supportive analysis has been added which will count all subjects with missing Week 24 SALT assessments, regardless of the reason, as non-responders. Rationale: This change has been made to mitigate the impact of missed SALT assessments at Week 24 due to COVID-19. • In the Protocol Summary – Statistical Methods and in Section 9.2.3, Analysis of Secondary Endpoints, the procedure for handling of missing data for binary endpoints was updated to exclude subjects from the analysis of secondary endpoints for any visit for which the assessment is missing due to COVID-19 related reasons. Subjects with assessments missing for other reasons will be counted as non-responders. Rationale: This change has been made to mitigate the impact of missed assessments due to COVID-19 and is consistent with the handling of missing data for the primary endpoint. • In Section 1.4, Clinical Experience, references were added to reference the clinical study reports or the clinical protocols for the following Pfizer studies: B7931005, B7981005, B7981006, B7981007, B7981019, and B7981032. Rationale: This change has been made to correct an error of omission. • In Sections 4.2, Exclusion Criteria and 5.8.2, Prohibited Medications and Treatments, the prohibition of medications that prolong the time from the beginning of the QRS complex to the end of the T wave (QT interval) was removed. Rationale: Pfizer has performed an analysis of nonclinical and clinical data, which indicate that there is no evidence of any clinically relevant QT interval prolongation due to PF-06651600 and therefore the risk for PF-06651600 to cause QT prolongation in humans is low. Prohibition of these medications is no longer required. • In Sections 5.8.3, Vaccinations, language was added to provide clarification on the use of COVID-19 vaccines. Rationale: This change was necessary due to the wide-spread use of COVID-19 vaccines globally in the setting of the COVID-19 pandemic. • In Section 9.2.2 Analysis of the Primary and Key Secondary Endpoints, the details of the “tipping point analysis” were removed. Rationale: The details of these analysis will be included in the Statistical Analysis Plan. • In Section 9.2.2.3 Per-Protocol Analysis (Analysis of the Primary and Key Secondary Endpoints), language was added detailing the protocol deviations which will be evaluated for each subject prior to unblinding to

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		determine if a subject will be excluded from the Per Protocol Analysis Set (PPAS). Rationale: Feedback from the FDA requested that the criteria used to define the per protocol analysis population be included in the protocol. • Section 9.2.3, Analysis of Secondary Endpoints, was revised to clarify how secondary endpoints that are not α-controlled will be analyzed. In addition, Information from former Section 9.2.2.1, Analysis of the Primary Endpoint to Assess the Secondary Objective, was moved to new Section 9.2.3.1 and retitled Analysis of Exposure-Response. Rationale: These changes were made to align with the reorganization of the endpoints for the study. • Section 9.2.5 Subgroup Analysis was added to check for consistency of key efficacy results from across subgroups which will also support the International Council for Harmonisation (ICH) E17 (General Principles for Planning and Design of Multi-Regional Clinical Trials) registration approach, as applicable. Rationale: The descriptive subgroup analyses will support the evaluation of consistency of treatment effect across subsets. • Added Section 9.4, Pharmacokinetic/Pharmacodynamic Early Unblinding, to provide details regarding early unblinding of the PK/PD data that is planned when ≥90% of subjects have reached 24 weeks post-randomization (or discontinued prior to the Week 24 visit). Access to the unblinded data will be limited to the list of PK/PD analysts and programmers that will be appropriately documented on the early unblinding for PK/PD form. Rationale: Early unblinding of the PK/PD data will enable PK and concentration/response model building for study readout. • In Appendix 1, Abbreviations, news abbreviations were added for "body mass index" or "BMI"; "Japan Pharmaceuticals and Medical Devices Agency" or "PMDA"; "United States Food and Drug Administration" or "FDA"; and "generalized linear mixed model" or "GLMM". Rationale: This change was made for clarification. • Removed Appendices 5 through 17 (Severity of Alopecia Tool [SALT], Columbia Suicide Severity Rating Scale [C-SSRS], AAPPO [Alopecia Areata Patient Priority Outcomes], Patient's Global Impression of Change [PGI-C], Patient Satisfaction with Hair Growth [P-Sat], Hospital Anxiety and Depression Scale [HADS], EuroQol 5 Dimensions [EQ-5D-5L], EuroQol 5 Dimensions – Youth [EQ-5D-Y], Patient Health Questionnaire – 8 Items [PHQ-8], 36-Item Short Form Health Survey Version 2 Acute [SF-36v2 Acute], Alopecia Areata Resource Utilization [AARU], Work Productivity and Activity Impairment: Alopecia Areata [WPAI:AA], and Clinician Global Impression – Alopecia Areata [CGI-AA]) as well as cross-references to the deleted appendices. Remaining appendices were renumbered as needed due to the deletions. Rationale: Updated per current practice not to include copyrighted instruments in protocol appendices. • In Appendix 6.3, Alternative Facilities for Safety Assessments, Table 8 was updated from "Windows for Remote Visits and Laboratory Sample Collections if Required Due to COVID-19 Disruptions" to "Windows for

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		Remote Visits and Laboratory Sample Collections if Required Due to Disruptions from Public Emergencies". Rationale: This change was made for clarification. • Throughout the document, references to the European Union (EU) (including VHP countries) were updated to European Medicines Agency (EMA) and competent authorities in the VHP countries, as applicable. Rationale: This change was made for clarification. • Throughout the document, references to table numbers were updated to reflect the addition of Tables 4, 5, 6, and 7 and figure numbers were updated to reflect the reorganization of the figures in Section 9.2.1. Rationale: This change was made for correctness of numbering of in-text tables and figures. • Global corrections to typographical errors, abbreviations, and definitions were made.
Amendment 4	20 October 2020	• Throughout the protocol, it has been specifically clarified that for the European Union (EU) (including the Voluntary Harmonisation Procedure [VHP] countries), the primary objective and primary endpoint will utilize an absolute Severity of Alopecia Tool (SALT) Score of ≤10 and not ≤20 at Week 24. Rationale: While this was previously included in the protocol (to use either SALT ≤10 or ≤20 for the primary objective and endpoint based on regulatory feedback), these changes have been made to align with a regulatory agency request to specify that SALT ≤10 will be used in the EU. • Throughout the protocol, it has been specifically clarified that for the EU (including VHP countries), the evaluation of the effect of PF-06651600 on patient centered outcomes (as measured by Patient's Global Impression of Change [PGI-C] response at Week 24) is a key secondary objective. The PGI-C response at Week 24 will be analyzed as a key secondary endpoint utilizing an appropriate testing procedure to control overall Type I error. Rationale: While it was previously included in the protocol that the PGI-C response will be analyzed as a key secondary endpoint utilizing an appropriate testing procedure to control overall Type I error in a separate analysis where required, these changes have been made to specify that in the EU PGI-C response will be analyzed as a key secondary endpoint. • Throughout the protocol, footnotes d and e in the Objectives and Endpoints tables were updated to clarify which secondary endpoints will be controlled for Type I error based on which SALT parameter at Week 24 (ie, ≤20 or ≤10) is utilized as the primary endpoint. Rationale: While this was previously included in the protocol, the footnotes have been revised for clarity. • Throughout the protocol, footnote g in the Objectives and Endpoints tables was updated to clarify that for the EU (including VHP countries), the endpoints utilizing the HADS will be analyzed as secondary endpoints. Rationale: While this was previously included in the protocol, the footnotes have been revised to specify that in the EU the HADS will be analyzed as secondary endpoints.

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Amendment 3	14 July 2020	• Throughout the protocol, the primary objective and the primary endpoint were changed from absolute severity of alopecia tool (SALT) score of "≤10" to "≤20". It has also been noted that "Response based on an absolute SALT Score ≤10 at Week 24" will be analyzed as the primary endpoint in a separate analysis where required. Rationale: These changes have been made to align with newly published literature (Wyrwich et al, 2020) and new feedback from clinical experts in alopecia areata that SALT ≤20 best distinguishes treatment success from lack of success, from the perspective of both clinicians and patients. These changes have been made after consultation with a regulatory agency. • Throughout the protocol, the secondary endpoint to characterize the exposure response was changed from absolute SALT score of "≤10" to "≤20". It has also been noted that where regulatory agencies require SALT ≤10 to be utilized for the primary endpoint, exposure response will also be analyzed utilizing SALT ≤10 in a separate analysis. Rationale: These changes have been made to align with changes to the primary endpoint. • Throughout the protocol, secondary endpoints were updated to include: • SALT score ≤10 at all timepoints (except at Week 24 if SALT ≤10 is the primary endpoint); • SALT score ≤20 at all timepoints (except at Week 24 if SALT ≤20 is the primary endpoint); • Change from baseline in SALT scores at all timepoints. Language was also added to indicate that if requested by specific regulatory agencies, SALT score ≤20 at Weeks 4, 8, 12, and 18 and SALT score ≤10 at Week 24 will be analyzed as secondary endpoints with Type I error control. Rationale: These changes have been made to align with changes to the primary endpoint. • Throughout the protocol, the secondary endpoint for 90% improvement in SALT score from baseline was removed. Rationale: This change has been made to reduce redundancy between 90% improvement in SALT and SALT ≤10. • Throughout the protocol, a secondary endpoint was added to evaluate the Patient's Global Impression of Change (PGI-C) response defined as PGI-C score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40 and 48. In addition, an exploratory endpoint was added to evaluate the improvement on the PGI-C at Weeks 4, 8, 12, 18, 24, 34, 40, and 48. It was also noted that at the request of regulatory agencies, the PGI-C response at Week 24 will be analyzed as a key secondary endpoint utilizing an appropriate testing procedure to control overall Type I error in a separate analysis where required. Rationale: These changes have been made to align with regulatory agency feedback to include a patient-reported outcome measurement as a key secondary endpoint and to report on multiple aspects of this patient reported outcome.

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		• Throughout the protocol, language was added to indicate that the study may be unblinded once ≥90% of subjects have reached 24 weeks post-randomization (or discontinued prior to the Week 24 visit). This includes the addition of Section 9.6, Interim Analysis. Rationale: These changes are consistent with the study design (placebo-controlled through Week 24 after which all subjects will receive active investigational product); this data will be used for internal decision-making by the sponsor. • Throughout the protocol, "dose response" was updated to "exposure response". Rationale: These changes are made to ensure consistency throughout the document. • In the Protocol Summary – Objectives and Endpoints and in Section 2, Study Objectives and Endpoints, the following secondary endpoints were changed to exploratory endpoints: • 50% improvement from baseline in SALT score at all timepoints. • Absolute SALT score at all timepoints. • Change from baseline in Hospital Anxiety and Depression Scale (HADS) at Weeks 4, 8, 12, 24, and 48. • Change from baseline in 36-Item Short Form Health Survey version 2 Acute (SF36v2 Acute) at Weeks 4, 8, 12, 24, and 48. Language was also added to indicate that if required by specific regulatory agencies, HADS endpoints will be analyzed as secondary endpoints. Rationale: These changes were made to align with regulatory feedback to reduce the number of secondary endpoints. • In the Protocol Summary – Objectives and Endpoints and in Section 2, Study Objectives and Endpoints, reference to the specific domain scores were removed from secondary endpoint evaluating a change from baseline in the Alopecia Areata Patient Priority Outcomes (AAPPO). The scales are now described in section 7.8.1. Rationale: These changes have been made because the validation and scoring for this patient reported outcome has now been completed and this reflects the correct domain scales. • In the Protocol Summary – Objectives and Endpoints and in Section 2, Study Objectives and Endpoints, the exploratory endpoint (previously secondary endpoint) evaluating a change from baseline in the Hospital Anxiety and Depression Scale (HADS) was split into two separate endpoints to clarify that the depression and anxiety subscales will be analyzed separately. In addition, two new exploratory endpoints were added to assess an improvement in HADS subscale scores for anxiety and depression, respectively in subjects with baseline scores indicative of anxiety or depression. Rationale: These changes have been made to align with feedback from the developer's scoring manual and clinical experts in alopecia areata to analyze depression and anxiety separately and to measure a change in individual subscales. • In the Protocol Summary – Objectives and Endpoints and in Section 2, Study Objectives and Endpoints, the exploratory endpoint for Patient

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		Satisfaction with Hair Growth (P-Sat) was revised from a continuous score to a categorical assessment to accurately indicate a subject's categorical improvement at the item level. Rationale: These changes have been made because the scaling and scoring for this patient reported outcome is still in the process of being established. • In the Protocol Summary – Objectives and Endpoints and in Section 2, Study Objectives and Endpoints, footnotes d and e were revised to state that the Sponsor may also analyze SALT ≤10 and/or SALT ≤20 at other timepoints controlling for Type 1 error at the request of regulatory agencies. Rationale: The changes have been made to reflect that the decision on additional analysis of SALT ≤10 or SALT ≤20 will be made following consultation with regulatory agencies. • In the Protocol Summary – Study Design, and in Section 3, Study Design, language was added to describe the stratification of subjects during the randomization process. Rationale: This change has been made to align with regulatory feedback. No changes to the randomization process itself have been implemented. This change was previously communicated to sites in the protocol administrative change letter dated 26 June 2019. • Throughout the Protocol Summary – Statistical Methods, and throughout subsections of Section 9, Data Analysis/Statistical Methods, the description of the primary endpoint, the assumptions for sample size calculations, and the testing procedures for multiple comparisons were all updated to reflect the changes in the primary endpoint as well as elevation of the PGI-C as a key secondary endpoint where required. Rationale: These changes have been made to align with changes in the primary endpoint and key secondary endpoint. • In the Schedule of Activities, reference to Appendix 19, Alternative Measures During Public Emergencies, was added. Rationale: This change has been made to clarify alternative measures to accommodate study procedures during public emergencies, including the coronavirus disease 2019 (COVID-19) pandemic. This change was previously communicated to sites in the protocol administrative change letter dated 05 June 2020. • In Schedule of Activities (footnote #k) and in Section 7.5.5, Audiological Evaluation, language was added to indicate that all procedures for audiological evaluation must be performed according to the Audiometry Study Guide. Rationale: These changes have been made for clarification. • In Section 1.3, Nonclinical and Phase 1 Efficacy and Safety Data and Section 1.6, Dose Rationale, updated information was provided on non-clinical studies and the no observed adverse effect level (NOAEL). Rationale: These changes have been made to provide updated information to sites. • In Section 1.3, Nonclinical and Phase 1 Efficacy and Safety Data, a statement was added to indicate that if new information is available on drug-drug-interactions (DDI) demonstrating that prohibition of a

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		concomitant medication is no longer required, this information will be communicated to sites via an administrative letter. Rationale: This change has been made to clarify the process for updating prohibited medications based on emerging results from PF-06651600 DDI studies. • In Section 1.4, Clinical Experience, and Section 1.4.1, Phase 2a Study in Alopecia, information was updated to include new ongoing studies with PF-06651600. In addition, a statement was added to indicate that the final results of the Phase 2a study in subjects with alopecia areata (B7931005) are now available in the Investigator's Brochure. Rationale: This change has been made to provide updated information now available in the January 2020 Investigator's Brochure. • In Section 1.4.2, Phase 2a Study in Rheumatoid Arthritis, information was updated to include the dose of PF-06651600 utilized in the protocol. Rationale: This change has been made to align with information available in the January 2020 Investigator's Brochure. • In Section 4.2, Exclusion Criteria #6.c, language was updated to correct "a" to "the". Rationale: This change has been made to correct a typographic error. • Throughout the protocol, several updates were made to the list of prohibited medications: • Everolimus and ibrutinib were included in the list of examples of prohibited immunosuppressants. • All cytochrome P450 isoenzyme 3A (CYP3A) inhibitors and several sensitive and moderate CYP3A substrates were removed from the prohibited medications list. • A separate list was also added to clarify CYP3A inducers and substrates which are now permitted. • Guidance was provided on which medications that prolong QT interval are prohibited. Rationale: The changes to the list of prohibited CYP3A inhibitors and substrates were made to align with results from recent DDI studies. Other changes noted here have been made for clarification. • In Section 4.2, Exclusion Criteria #14 and Section 7.5.9, Varicella-Zoster Virus Immunoglobulin G Antibody (VZV IgG Ab) Testing, language was updated to reflect that subjects with documentation of vaccination (2 doses) can be enrolled even if VZV IgG Ab testing is negative. Rationale: This change has been made to ensure consistency with the Centers for Disease Control varicella vaccine recommendations, which state that commercial assays are not sensitive enough to always detect antibodies after vaccination. Documented receipt of 2 doses of varicella vaccine supersedes results of subsequent serologic testing. (https://www.cdc.gov/vaccines/vpd/varicella/hcp/recommendations.html, accessed 27Jan2020). • In Section 4.3.1, Contraception, bilateral tubal ligation was added to the list of highly effective contraceptive methods. Rationale: This change has been made for clarification; "bilateral tubal occlusion" already listed in this section was intended to encompass the

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		procedures for both bilateral tubal occlusion and bilateral tubal ligation since both prevent ova from moving through the fallopian tubes, thereby preventing contact with sperm. This change was previously communicated to sites in the protocol administrative change letter dated 06 November 2019. • In Section 6.1, Screening, Visit 1, clarifications were made to information collected on history of alcohol consumption and of previous drug treatments for alopecia areata (AA). Rationale: These changes have been made for clarification. These changes were previously communicated to sites in the protocol administrative change letter dated 11 October 2019. • In Section 7, Assessments, reference to Appendix 19, Alternative Measures During Public Emergencies, was added. Rationale: This change has been made to clarify alternative measures to accommodate study procedures during public emergencies, including the COVID-19 pandemic. This change was previously communicated to sites in the protocol administrative change letter dated 05 June 2020. • In Section 7.5.1, Vital Signs, language was updated to allow the use of temporal artery temperature measurements. Rationale: This change has been made to reflect current clinical practice for temperature measurement. • In Section 7.5.6.2.2, Potential Drug-Related Rash and Unexplained Rash, the title was updated to include "Potential" drug-related rashes and "Unexplained Rash". Rationale: This update was made for clarification. • In Section 7.5.12, Events for Adjudication/Review Committee Submission, language was added to indicate that additional types of events, not already listed in the protocol, may be adjudicated. Rationale: This change was made to allow for addition types of events to be requested for review and adjudication. • In Section 7.8.1, Alopecia Areata Patient Priority Outcomes (AAPPO), language was updated to correct "psychological" to "emotional" to more accurately reflect the concepts being measured by the AAPPO. In addition, language was relocated from Section 9.2.4, Analysis of Other Endpoints, to this section providing information on the anchor-based methodology to be used for interpretation of the AAPPO. Rationale: This change has been made for clarification. • In Section 7.8.4, Hospital Anxiety and Depression Scale (HADS), language was updated to correct the description of the subscales for the HADS. Rationale: This change has been to limit any observer bias at sites. • In Section 7.11.1, Samples for Interferon Gamma-Induced Protein – 10 (IP-10) Analysis, a statement was added to indicate that IP-10 samples will not be collected if the exportation of these samples from the country of origin is prohibited by local regulations or institutional review board (IRB)/ethics committee (EC) decision. Rationale: This change was made to align with a decision from one country's local Good Clinical Practices (GCP) office to prohibit the exportation of IP-10 samples from within the country of origin to the

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		central laboratory for analysis. This change was previously communicated to sites in the protocol administrative change letter dated 18 July 2019. • Throughout the subsections of Section 9, Data Analysis/Statistical Methods, language was added to describe the testing method for controlling the Type I error for SALT ≤10 with a primary endpoint of SALT ≤20. Rationale: These changes have been made to align with changes in the primary endpoint and key secondary endpoint. • Section 9.1.1, Efficacy Analysis changed to Section 9.2 and subsequent sections within Section 9 were appropriately renumbered. Rationale: Change made to align with protocol template section numbering requirements. • In Section 9.2.1, Testing Procedure for Multiple Comparisons, the following statement was removed "If the observed p-values after accounting for the test procedure is ≤0.00125, it will be concluded that PF-06651600 demonstrates 'clear and compelling' evidence of effectiveness in treating moderate to severe AA patients as measured by the primary endpoint." Rationale: There is no single p-value that will be accepted in all regions. While additional statistical thresholds may be considered during regulatory reviews, it is not appropriate to include in the protocol. • In Section 9.2.2, Analysis of the Primary Endpoint, language was added to indicate the key criteria used to define a per-protocol analysis that will be performed for the primary endpoint. Rationale: These changes have been made to align with regulatory feedback. • In Section 9.2.4, Analysis of Other Endpoints, language was revised to reflect that other endpoints will not be analyzed using the same procedure as the primary endpoint; instead they will be analyzed using descriptive statistics. In addition, the language describing the anchor-based methodology to be used for interpretation of the AAPPO was revised and relocated to Section 7.8.1, Alopecia Areata Patient Priority Outcomes (AAPPO). Rationale: This change was made for clarification. • Section 9.7, Data Monitoring Committee, was renumbered (previously Section 9.6) to allow for inclusion of new section 9.6, Interim Analysis. Rationale: These changes have been made for administrative purposes. • In Section 15.1, Communication of Results by Pfizer, language was revised to align with updated Pfizer template language on public disclosure of clinical trial results. Rationale: This change has been made to align with updated Pfizer protocol template language. • In Section 16, References (#59), and in Appendix 2, Hepatitis B Testing Algorithm and Full Eligibility Criteria, a correction has been made to the reference for Hepatitis B virus global prevalence. Rationale: These changes have been made to correct typographic errors. • In Section 16, References, a new reference #87 was added to support the clarification that the analysis of the HADS depression and anxiety

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		subscales should be performed separately to align with feedback from the developer's scoring manual. Rationale: This change has been made to support the updates in the analysis of the HADS scores. • In Section 16, References, a new reference #88 was added to support the addition of exploratory endpoints that evaluate proportion of subjects who achieve 'normal' anxiety and depression subscale among subjects with abnormal scores at baseline. Rationale: This change has been made to support the changes in the analysis of the HADS scores. • In Section 16, References, a new reference #89 was added to provide a reference for SALT ≤20 as a clinically meaningful treatment effect. Rationale: This change has been made to support the change to the primary endpoint. • In Appendix 1, Abbreviations, new abbreviations were added for: "Brainstem auditory evoked potentials" or "BAEP"; "Coronavirus disease 2019" or "COVID-19"; "Contract research organization" or "CRO"; "Clinical study report" or "CSR"; "Cytochrome P450 isoenzyme 3A" or "CYP3A"; "European Medicines Agency" or "EMA"; "Per Protocol Analysis Set" or "PPAS"; "50% improvement in SALT score from baseline" or "SALT50"; "75% improvement in SALT score from baseline" or "SALT75"; "Severe acute respiratory syndrome coronavirus 2" or "SARS-CoV2"; "Torsades de pointes" or "TdP". Rationale: These changes have been made for clarification. • Appendix 3.1, Monitoring, and Appendix 3.2, Discontinuation, all references to "creatinine kinase" were updated to "creatine kinase"." to correct a typographic error. Rationale: These changes have been made to correct a typographical error. • In Appendix 3.1, Monitoring, and Appendix 3.2, Discontinuation, language was added to provide clarification regarding the timelines for re-testing of laboratory values. Rationale: These changes have been made for clarification. • Appendix 3.2, Discontinuation, updated discontinuation criterion for ECG findings to clarify that an "increase" from baseline in QTcF of >60 milliseconds requires discontinuation. A decrease of this amount does not require discontinuation. Rationale: These changes have been made for clarification. • Appendix 19, Alternative Measures During Public Emergencies, was added. Rationale: This change has been made to clarify alternative measures to accommodate study procedures during the public emergencies, including

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		the COVID-19 pandemic. This change was previously communicated to sites in the protocol administrative change letter dated 05 June 2020.
Amendment 2	30 May 2019	• Voluntary Harmonisation Procedure (VHP) was added to the list of abbreviations. The VHP countries participating in this study are Czech Republic, Germany, Hungary, Poland, and Spain. • In the Schedule of Activities, "Contraception check for WOCBP" was updated to "Contraception check, as applicable". Rationale: This change was made to align with a request from the VHP to require male subjects in VHP countries in the EU to use a barrier method of contraception during heterosexual intercourse. • In the Schedule of Activities, footnote p was updated to indicate that at sites in VHP countries in the European Union (EU) female subjects of childbearing potential will be instructed to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44). Rationale: This change was made to align with a request from the VHP to include more frequent pregnancy testing for females of childbearing potential in VHP countries in the EU. • In the Schedule of Activities, footnote dd was updated to indicate that pregnancy tests should be performed "according to the Schedule of Activities" instead of "at every visit". Rationale: This change was made to ensure consistency with the Schedule of Activities. • In Section 1.7, Summary of Benefit/Risk Assessment, the phrase "Men in the study are not required to use birth control because" was deleted. Rationale: This change was made to align with a request from the VHP to require male subjects in VHP countries in the EU to use a barrier method of contraception during heterosexual intercourse. • In Section 4, Subject Eligibility Criteria, a statement was added to explain that there are certain eligibility requirements specific to the VHP countries in the EU and to include the list of participating VHP countries. Rationale: This change was made for clarification of VHP-specific requirements for eligibility. • In Section 4.1, Inclusion Criteria, criterion #3 was updated to "Male or female subjects age 12 years and older, inclusive, at time of informed consent/assent. Adolescent subjects below the age of 18 years will only be enrolled into this study if permitted by the sponsor, local competent authority, and institutional review board (IRB)/ethics committee (EC). Otherwise, only subjects 18 years or older (or age specified by applicable reviewer) will be enrolled in those countries, regions, or sites. Within VHP countries in the EU, subjects must be aged 18 through 74 years at the time of informed consent." Rationale: This change was made to align with a request from the VHP to exclude subjects age 75 years and older in VHP countries in the EU. • In Section 4.1, Inclusion Criteria, criterion #4 was updated to include male reproductive safety requirements. Specifically, it indicates that in VHP countries in the EU male subjects should use a male condom during sexual intercourse with females of childbearing potential and should refrain from donating sperm during the study and for 90 days after the last dose of study

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		intervention. Language was also added to clarify that there are no such requirements outside of VHP countries in the EU. Rationale: This change was made to align with a request from the VHP to require male subjects in VHP countries in the EU to use a barrier method of contraception during heterosexual intercourse and to refrain from donating sperm during the relevant period. • In Section 4.1, Inclusion Criteria, criterion #4.b, bullet 3 (Postmenopausal female) was updated to "A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a high follicle stimulating hormone (FSH) level in the postmenopausal range must also be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or hormone replacement therapy (HRT). Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment." The requirement for follicle stimulating hormone (FSH) testing has not changed. Rationale: This change was made to align with a request from the VHP to update the definition of "postmenopausal state". • In Section 4.2, Exclusion Criteria, criterion #8.i, a reference was added for the website www.CredibleMeds.org. Subsequent references were renumbered as appropriate. Rationale: This change was made to correct an omission of the reference. • In Section 4.3.1, Contraception, language was added to indicate that in VHP countries in the EU male subjects should use a male condom during sexual intercourse with a female of childbearing potential and should refrain from donating sperm during the study for 90 days after the last dose of study intervention. Language was also added to clarify that there are no such requirements outside of VHP countries in the EU. Rationale: This change was made to align with a request from the VHP to require male subjects in VHP countries in the EU to use a barrier method of contraception during heterosexual intercourse and to refrain from donating sperm during the relevant period. • In Section 6, Study Procedures, paragraph 3 was added to indicate that at sites in VHP countries in the EU female subjects of childbearing potential will be instructed to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44). Rationale: This change was made to align with a request from the VHP to include more frequent pregnancy testing for females of childbearing potential in VHP countries in the EU. • In Section 6.2.11, Visit 12, Day 281/ Week 40 (±7 days), bullet 6 was updated to indicate that at sites in VHP countries in the EU female subjects of childbearing potential will be instructed to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44).

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		Rationale: This change was made to align with a request from the VHP to include more frequent pregnancy testing for females of childbearing potential in VHP countries in the EU. • In Section 7.1, Check for Initiation of Menarche (for Premenarchal Females Only), the language was updated to indicate that pregnancy tests should be performed "according to the Schedule of Activities" instead of "at every visit". Rationale: This change was made to ensure consistency with the Schedule of Activities. • In Section 7.2, Pregnancy Testing, the third paragraph was added to indicate that at sites in VHP countries in the EU female subjects of childbearing potential will be instructed to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44). Rationale: This change was made to align with a request from the VHP to include more frequent pregnancy testing for females of childbearing potential in VHP countries in the EU. • In Section 7.5.8.1, Purified Protein Derivative (PPD) Test, a typographic error in paragraph 2 was corrected to reflect that the test should be performed and interpreted as "negative" (not "positive") according to local standards. Rationale: This clarification was made to correct a typographic error and was previously communicated to active sites in the protocol administrative change letter dated 18-Apr-2019. • In Section 9, Data Analysis/Statistical Methods was updated to include more specific information on the timing of the finalization of the statistical analysis plan (SAP). Rationale: This change was made to align with a request from the VHP to provide information on when the SAP would be finalized. In Appendix 3, Guidelines for Subject Safety Monitoring and Discontinuation, a typographic error in the monitoring criteria for hemoglobin was corrected to reflect that a decrease greater than or equal to 2.0 g/dL (not just a decrease of 2.0 g/dL) requires additional monitoring activities. Rationale: This clarification was made to correct a typographic error and was previously communicated to active sites in the protocol administrative change letter dated 18-Apr-2019. • In Appendix 5, Severity of Alopecia Tool (SALT), typographic errors were corrected in the calculations shown for the first example. Rationale: This clarification was made to correct a typographic error.
Amendment 1	28 February 2019	• Throughout the protocol, text has been updated to clarify Japan-specific requirements for Hepatitis B testing, which have been added to Appendix 18.1 under country-specific requirements, specifically, in the Schedule of Activities (footnotes r and s), Exclusion Criterion #20, Section 6.1 (screening visit), Section 7.5.7 (footnotes d and e for Table 3), Section 7.5.11, and Appendix 2. Rationale: This clarification was made to align with local regulations in Japan which require that Hepatitis B surface antibody testing be included in the initial screening for Hepatitis B testing and not in reflex testing. • Throughout the protocol, the text has been updated to change "audiogram" to "audiological evaluation" and to provide additional details on the

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		required evaluations, specifically in the Schedule of Activities (footnote k) and Section 7.5.5, Audiogram. Rationale: This clarification was made to provide a high level summary of the tests required for audiological evaluation detailed in the Audiometry Study Guide. • Throughout the protocol, "CYP3A4" was updated to "CYP3A" in all references to excluded/prohibited medications. In addition, Exclusion Criteria for use of CYP3A4 inducers were updated to reflect a washout period of 4 weeks (or 28 days). Rationale: These clarifications were made as the language in the body of the protocol was previously inconsistent with Appendix 4. There are no changes to the medications that are excluded/prohibited. • Exploratory Endpoints for Patient's Global Impression of Change (PGI-C) and Patient Satisfaction with Hair Growth (P-Sat) have been updated from "Change from baseline in" to "Absolute score of". Rationale: This clarification was made as the questionnaires themselves report on a change from baseline. • Throughout the protocol, an assessment was added to address a new exploratory endpoint. The Clinician Global Impression – Alopecia Areata (CGI-AA) was added to the Protocol Summary, Schedule of Activities, Section 2, Study Objectives and Endpoints, Section 6, Study Procedures, Section 7.6.5, Clinician Global Impression – Alopecia Areata (CGI-AA), Section 7.12, Rater Qualifications, and Appendix 17, Clinician Global Impression – Alopecia Areata (CGI-AA). Rationale: The addition of this clinician reported outcome assessment will provide an additional anchor for validation of the Severity of Alopecia Tool (SALT) and will provide information on concordance or discordance between patient and clinician perspectives. • Throughout the protocol, the assessment of both the Patient's Global Impression of Change (PGI-C) and the Patient's Impression of Satisfaction (P-Sat) were removed from the Day 1 visit. Rationale: These questionnaires themselves report on a change from baseline; therefore, there is no need to capture a baseline assessment. • Throughout the protocol, the method of body temperature evaluation was updated to include "axillary". Rationale: This clarification was made to correct an error of omission. • In Section 1.4.1, Phase 2a Study in Alopecia, information was updated to reflect changes in the Phase 2a study design, changing the single-blind extension phase into an open-label extension phase. • In Section 1.7, Summary of Benefit/Risk Assessment, information on fertility was updated. Rationale: This change was made in response to new data available in the Investigator's Brochure. • In Section 4.1, Inclusion Criterion #3 was updated to "Male or female subjects age 12 years and older, inclusive, at time of informed consent/assent. Adolescent subjects below the age of 18 years will only be enrolled into this study if permitted by the sponsor, local competent authority, and institutional review board (IRB)/ethics committee

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		(EC). Otherwise, only subjects 18 years or older (or age specified by applicable reviewer) will be enrolled in those countries, regions, or sites." Rationale: This clarification was made to indicate that IRBs/ECs could render a decision on the inclusion of adolescents at a site level (in addition to local competent authorities and the Sponsor). • In Section 4.1, Inclusion Criterion #6 was updated from "must" to "should". Rationale: This change is to accommodate the use of some ad hoc medications (eg, those medications used for headache, menstrual cramps, etc). • In Section 4.2, Exclusion Criterion #8 sub-bullet d was updated to "5α-Reductase inhibitors (5-ARIs) (eg, finasteride, dutasteride)". In addition, "oral minoxidil" and "spironolactone if used specifically for alopecia areata" were also added to examples of systemic treatments that could affect AA. These changes were also reflected in Section 5.8.2, Prohibited Medications and Treatments. Rationale: These clarifications were made to provide more specific examples of prohibited systemic treatments. • In Section 4.2, Exclusion Criterion #8 sub-bullet f was updated to include "topical irritants (eg, anthralin) and liquid nitrogen cryotherapy". These changes were also reflected in Section 5.8.2, Prohibited Medications and Treatments. Rationale: These clarifications were made to provide more specific examples of prohibited topical treatments. • In Section 4.2, Exclusion Criterion #14 was updated to clarify the eligibility requirements for adolescents regarding varicella exposure. This clarification was also reflected in the Schedule of Activities, Section 6.1, Screening, Visit 1, Section 7.5.7, Clinical Laboratory Tests, and Section 7.5.9, Varicella-Zoster Virus Immunoglobulin G Antibody (VZV IgG Ab) Testing. Rationale: This clarification was made to provide specific information on the number of required doses of varicella vaccination and to avoid any confusion as to how the eligibility criteria related to vaccination records and varicella-zoster virus immunoglobulin G antibody results should be applied. • In Section 4.2, Exclusion Criterion #21 after sub-bullet c was updated to add the following sentence: "A subject who is currently being treated for active TB infection must be excluded from the study." Rationale: This clarification was made to provide specific guidance on subjects with active TB infection. Active infection was already excluded under criterion #16; however, this language was added to #21 as well for clarity. • In Section 4.2, Exclusion Criterion #24 sub-bullet c was updated to "Platelet count $<150 \times 10^9$/L or $<150{,}000/mm^3$". Rationale: This change was made to correct a typographic error. This change was previously communicated to active sites in the protocol administrative letter dated 16-Nov-2018.

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		• In Section 4.3.1, Contraception, the allowable methods of contraception were updated to include the use of combination hormonal contraceptives in combination with a barrier method. Rationale: This change has been made based on the results of the drug-drug-interaction study B7981018. Further information is available in the current version of the Investigator's Brochure (IB). • In Section 5.8.1, Permitted Concomitant Medications, the dose of acetaminophen was updated from "1.5 g/day" to "3 g/day". Rationale: This change was made to better align with the dosing instructions for acetaminophen. • In Section 5.8.4, Surgery, the following text was added for clarity: "Subjects who do have elective surgery should temporarily discontinue study intervention for 1 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." Rationale: This change was made to provide sites with specific instructions on how to manage dosing of investigational product in the event that a subject requires surgery during the study. • In Section 6.1, Screening, Visit 1, clarified that audiological evaluation can be performed within 8 weeks of Day 1. Rationale: This is a clarification to ensure consistency with language in the Schedule of Activities and in Section 7.5.5, Audiological Evaluation. • In Section 6.3.2, Early Termination (ET) Visit, and Schedule of Activities, the IP-10 assessment has been deleted at the ET visit. Rationale: IP-10 sampling has been removed from the ET visit due to the intended collection of these samples only up to Week 24, as well as due to expected differences in timing of the prior dose of study drug relative to IP-10 sampling under early termination circumstances which could reduce their value in pharmacodynamic analyses. • In Section 7.5.6.2.2, Drug Related Rash, the following text was added "In addition, the subject 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)". Rationale: The text was added for clarification of requirements for assessment of drug-related rash which were detailed in other supporting documentation. • In Section 7.5.6.2.2, Drug Related Rash, the text has clarified tests performed and that results are forwarded to the Sponsor. Rationale: This change was made to correct a typographic error and/or omission. • In Section 7.6.1, Severity of Alopecia Tool (SALT), the text has been clarified. Rationale: This language was reworded for clarity. • In Section 7.5.7, Table 3, Varicella-zoster virus immunoglobulin G antibody (VZV IgG Ab) testing was added to the table. Rationale: This change as made to correct a typographic error.

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		• In Appendix 3.2, Discontinuation, text on how to handle subjects with a clinically meaningful decline in hearing has been updated. Rationale: The clarification was made to align with instructions included in the Audiometry Study Guide. • In Appendix 4, Prohibited Concomitant Medications, text has been updated to indicate that amiodarone and mitotane can be used in an emergency situation, but the subject must then be discontinued from the study. Rationale: This clarification was made to provide specific information on how to handle emergency situations requiring these two medications. • In Appendix 12, EuroQoL 5 Dimensions-Youth (EQ5D Y), the second page of the questionnaire has been added. Rationale: This change was made to correct a typographic error. • Global corrections to typographical errors, abbreviations, and definitions were made.
Original protocol	17 September 2018	Not applicable (N/A)

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

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PROTOCOL SUMMARY

Background and Rationale:

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

$CD8^+$ T cells, 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).[7,9] 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.[1] IL-12 and IL-23 may also play a role in the pathogenesis of AA.[11]

Clinical presentation of AA can be limited to small, circular patches of scalp hair loss (patchy hair loss, alopecia focalis), involve complete loss of hair on the scalp (alopecia totalis [AT]), or total loss of hair on the scalp and body (alopecia universalis [AU]).[12] AA involving 50% or greater scalp hair loss, including AT and AU, is considered an advanced form of alopecia, according to the United States (US) National Alopecia Areata Foundation.[13] 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. It is estimated that AA affects as many as 6 to 7 million individuals in the US[8] and 147 million worldwide.[13] AA is a disease with a significant pediatric prevalence, in addition to the burden of disease seen in adults. 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,[21-25] problems with social relations,[26] decreased health-related quality of life (HRQoL) and general quality of life (QoL), as well as the QoL of their families.[27-35]

No drugs have been approved for the treatment of AA in most countries/regions, including the US and the European Union (EU). Review of 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. However, there is neither a cure for AA, nor is there a therapy convincingly demonstrated to induce and sustain remission long term.[38-42]

PF-06651600 is an orally bioavailable, small molecule that is currently being investigated in patients with AA. PF-06651600 inhibits, by irreversibly blocking the adenosine triphosphate (ATP) binding site, Janus kinase 3 (JAK3) and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family (BTK, BMX, ITK, TEC, TXK), with high selectivity over the other three JAK isoforms, JAK1, JAK2, and tyrosine kinase 2 [TYK2], as well as over the broader kinome. PF-06651600 potently inhibits signaling of the common γ-chain receptors for IL-15 and IL-21, which have been implicated in the pathogenic pathways of AA.[1] Additionally, PF-06651600 inhibits the cytotoxic function of $CD8^+$ T cells

and NK cells which have also been implicated in the pathogenic process of AA.[2,3] This inhibition may be mediated through mechanisms dependent on JAK3 and TEC kinase family members.[4,5,6]

Objectives and Endpoints:

The following table details the overall study objectives and endpoints. There are some region specific differences noted throughout. Table 5 in Section 9 lists the primary and secondary endpoints of the study organized by known regional requirements.

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 compared to placebo in adult and adolescent alopecia areata (AA) subjects with 50% or greater scalp hair loss on regrowth of lost hair (as measured by an absolute Severity of Alopecia Tool (SALT) Score ≤20) at Week 24. Note: For the European Medicines Agency (EMA) and competent authorities in the Voluntary Harmonisation Procedure (VHP) countries,[a] the primary objective is to evaluate the efficacy of PF-06651600 compared to placebo in adult and adolescent AA subjects with 50% or greater scalp hair loss on regrowth of lost hair (as measured by an absolute SALT Score ≤10) at Week 24.	• Response based on an absolute SALT Score ≤20 at Week 24. Note: For the EMA and competent authorities in the VHP countries, response based on an absolute SALT Score ≤10 at Week 24 will be analyzed as the primary endpoint in a separate analysis.
Key Secondary Objective(s):	**Key Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 compared to placebo in adult and adolescent AA subjects with 50% or greater scalp hair loss on regrowth of lost hair (as measured by an absolute SALT Score ≤10) at Week 24. Note: This key secondary objective will be utilized as the primary objective for the EMA and competent authorities in the VHP countries. Additionally, this key secondary objective will not apply for the United States Food and Drug Administration (FDA) /Japan Pharmaceuticals and Medical Devices Agency (PMDA).	• Response based on an absolute SALT Score ≤10 at Week 24. Note: This key secondary endpoint will be utilized as the primary endpoint for the EMA and competent authorities in the VHP countries. Additionally, this key secondary endpoint will not apply for the FDA/PMDA.
• To evaluate the effect of PF-06651600 on patient centered outcomes (as measured by PGI-C response) at Week 24. Note: This key secondary objective is only applicable for the EMA and competent authorities in the VHP countries.	• PGI-C response defined as a score of "moderately improved" or "greatly improved" at Week 24. Note: This key secondary endpoint is only applicable for the EMA and competent authorities in the VHP countries.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To characterize the exposure response of PF-06651600 on regrowth of lost hair.	• Response based on an absolute SALT Score ≤20 at Week 24 will be used to characterize the exposure response.[b]

• To assess the efficacy of PF-06651600 on regrowth of lost hair during the treatment period over time.	• Response based on an absolute SALT score ≤20 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48.[c,d] • Response based on an absolute SALT score of ≤10 at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.[e] • Response based on a 75% improvement in SALT score from baseline (SALT75) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Change from baseline in SALT scores at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Response based on at least a 2 grade improvement or a score of 3 in Eyebrow Assessment (EBA) score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Response based on at least a 2-grade improvement or a score of 3 in Eyelash Assessment (ELA) score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate the effect of PF-06651600 on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.[f]	• PGI-C response defined as a PGI-C score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.[f] • Change from baseline in Alopecia Areata Patient Priority Outcomes (AAPPO) scales at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.
Safety Objective(s)	**Safety Endpoint(s)**
• To evaluate the safety and tolerability of PF-06651600 in the treatment period over time.	• Incidence of treatment-emergent adverse events (AEs). • Incidence of serious AEs (SAEs) and AEs leading to discontinuation. • The incidence of clinically significant abnormalities in vital signs. • The incidence of clinically significant abnormalities in clinical laboratory values.
PK Objective(s)	**PK Endpoint(s)**
• To characterize pharmacokinetics of PF-06651600.	• Plasma concentrations of PF-06651600 at Weeks 4, and 8 or 12.
Exploratory Objective(s):	**Exploratory Endpoint(s):**
• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.

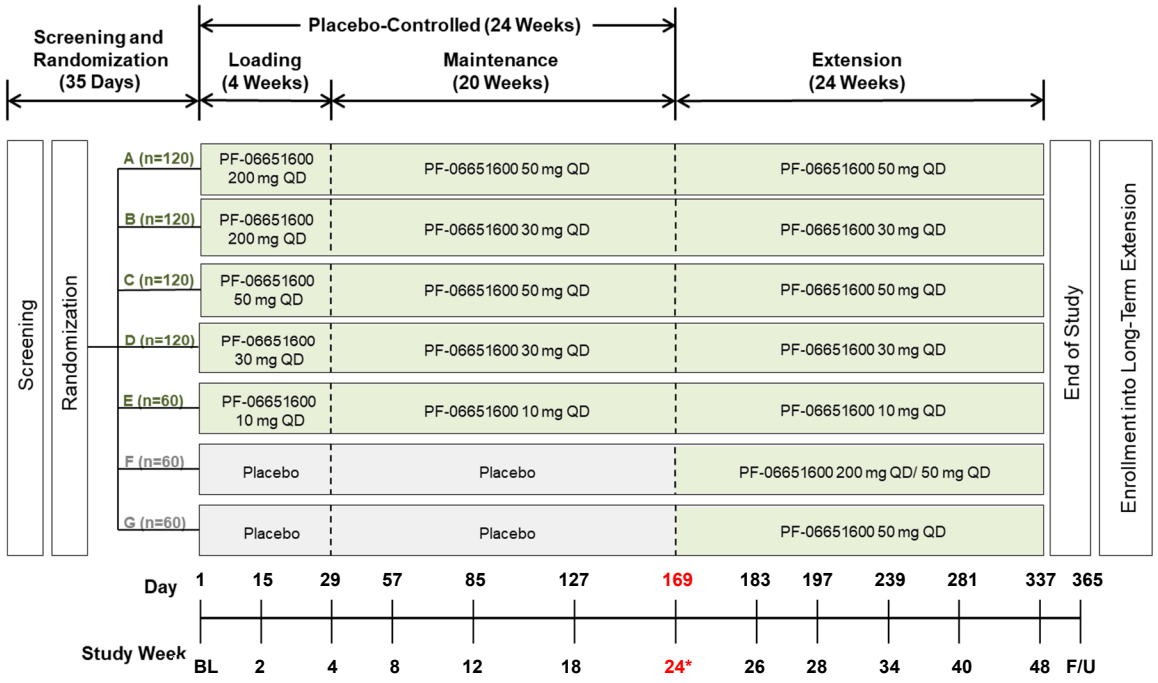
• To assess the efficacy of PF-06651600 on regrowth of lost hair during the treatment period over time.	• Response based on a 50% improvement in SALT score from baseline (SALT50) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Absolute SALT scores at Baseline, Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate the effect of PF-06651600 on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.	• Improvement on PGI-C defined as "slightly improved", "moderately improved", or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48. • Improvement on Patient Satisfaction with Hair Growth (P-Sat) items defined as slightly, moderately, or very satisfied at Weeks 4, 8, 12, 18, 24, 34, 40, and 48. • Change from baseline in EuroQoL 5 Dimensions (EQ-5D-5L) in adults or EuroQoL 5 Dimensions-Youth (EQ-5D-Y) in adolescents at Weeks 4, 12, 24, and 48. • Change from baseline in Alopecia Areata Resource Utilization (AARU) at Weeks 12, 24, 34, and 48. • Change from baseline in Work Productivity and Activity Impairment: Alopecia Areata (WPAI:AA) at Weeks 12, 24, 34, and 48. • Change from baseline in the depression subscale score of the Hospital Anxiety and Depression Scale (HADS) at Weeks 4, 8, 12, 24, and 48.[g,87] • Change from baseline in the anxiety subscale score of the HADS at Weeks 4, 8, 12, 24, and 48.[g,87] • Improvement on HADS among subjects with a baseline subscale score indicative of depression who achieved a "normal' subscale score indicative of an absence of depression at Weeks 4, 8, 12, 24, and 48.[g,79,88] • Improvement on HADS among subjects with a baseline subscale score indicative of anxiety who achieved a "normal' subscale score indicative of an absence of anxiety at Weeks 4, 8, 12, 24, and 48.[g,79,88] • Change from baseline in 36-Item Short Form Health Survey version 2 Acute (SF36v2 Acute) at Weeks 4, 8, 12, 24, and 48.
• To evaluate the effect of PF-06651600 on the clinician global impression of severity of scalp hair loss.	• Change from baseline in Clinician Global Impression – Alopecia Areata (CGI-AA) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate efficacy of PF-06651600 in AA nail disease over time.	• Change from baseline in fingernails affected by AA at Weeks 12, 24, 34, 40, and 48.

• To assess pharmacodynamic and disease-related biomarkers over time.	• Change from baseline in interferon gamma-induced protein 10 (IP-10) at Weeks 4, 8, 12, and 24. • Change from baseline in percent and absolute lymphocyte subsets (T-cell, B-cell, and natural killer [NK] cells) at Weeks 4, 12, 24, and 48. • Change from baseline in immunoglobulins (IgA, IgG, IgM) at Weeks 24 and 48.

a. The VHP countries participating in this study are Czech Republic, Germany, Hungary, Poland, and Spain.
b. For the EMA and competent authorities in the VHP countries, when SALT ≤10 is utilized for the primary endpoint, exposure response will be analyzed utilizing SALT ≤10 in a separate analysis.
c. For the EMA and competent authorities in the VHP countries, when SALT ≤10 is utilized for the primary endpoint, SALT ≤20 at Week 24 will be analyzed as a secondary endpoint.
d. When SALT ≤20 response at Week 24 is utilized as the primary endpoint, responses based on absolute SALT score ≤20 at Weeks 18, 12, 8 and 4 will be analyzed controlling for Type I error utilizing an appropriate testing procedure. When SALT ≤10 response at Week 24 is utilized as the primary endpoint, the response based on absolute SALT score ≤20 at Week 24 will be analyzed controlling for Type I error utilizing an appropriate testing procedure.
e. When SALT ≤20 response at Week 24 is utilized as the primary endpoint, the response based on absolute SALT score ≤10 at Week 24 will be analyzed controlling for Type I error utilizing an appropriate testing procedure. When SALT ≤10 response at Week 24 is utilized as the primary endpoint, the responses based on absolute SALT score ≤10 at Weeks 18, 12, 8 and 4 will be analyzed controlling for Type I error utilizing an appropriate testing procedure.
f. For the EMA and competent authorities in the VHP countries, the evaluation of the effect of PF-06651600 on patient centered outcomes (as measured by PGI-C response at Week 24) is a key secondary objective. The PGI-C response at Week 24 will be analyzed as a key secondary endpoint utilizing an appropriate testing procedure to control overall Type I error.
g. For the EMA and competent authorities in the VHP countries, endpoints utilizing the HADS will be analyzed as secondary endpoints.

Study Design:

This is a Phase 2b/3, randomized, double-blind, placebo-controlled, dose-ranging study to investigate PF-06651600 in AA. The study will have a maximum duration of approximately 57 weeks. This includes an up to 5-week Screening period, a 48-week treatment period, and a 4-week follow-up period as shown below. The treatment period will be comprised of a placebo-controlled period that includes a 4-week loading phase and a 20-week maintenance phase, followed by a 24-week extension phase. The study will enroll a total of approximately 660 subjects. The study will be conducted at approximately 120 sites.



* Primary endpoint is response based on absolute Severity of Alopecia Tool (SALT) Score ≤20 at Week 24.

To be eligible to enroll in this study, subjects must have moderate to severe AA with ≥50% hair loss of the scalp (Severity of Alopecia Tool [SALT] score ≥50) at both Screening and baseline visits, without evidence of terminal hair regrowth within the previous 6 months and with the current episode of hair loss ≤10 years.

Screening will occur within 35 days prior to the first dose of study drug to confirm that subjects meet selection criteria for the study. Eligible subjects will be randomized as described below.

A stratified randomization will be used for operational purposes in order to achieve a target global composition for AT/AU and adolescent subjects in the enrolled population. The targets for enrollment are approximately 40% AT/AU and approximately 15% adolescents. The randomization will be operationalized as follows. In regions enrolling both adolescents and adults, there will be four strata:

<18 years of age and AT/AU;

<18 years of age and not AT/AU;

≥18 years of age and AT/AU; and

≥18 years of age and not AT/AU.

Within each of these strata, subjects will be randomized in a 2:2:2:2:1:1:1 manner to blinded PF-06651600 and matching placebo for a total of 7 treatment sequences.

In regions enrolling only adults, there will be two strata:

≥18 years of age and AT/AU; and

≥18 years of age and not AT/AU.

In these regions, subjects will be randomized using the same ratio as described for regions enrolling both adolescents and adults.

All subjects will begin dosing during the loading phase according to their assigned sequence. Following the 4-week loading phase, subjects will continue dosing according to their assigned sequence in the 20-week maintenance phase. At the end of the maintenance phase, placebo-treated subjects will be advanced in a prespecified, blinded manner to one of 2 active treatment sequences for the remainder of the study (through Week 48). Investigators, subjects, and the sponsor study team will be blinded to treatment throughout the duration of the study. Following the last dose of study drug, both discontinued and completed subjects will enter into a 4-week follow-up period for safety monitoring. Subjects who complete treatment may be eligible for enrollment in a long-term study (Phase 3 study B7981032). Subjects who enroll immediately into the B7981032 study will not be required to complete the 4-week follow-up period in this study.

Study Treatments:

Blinded PF-06651600 and its matched placebo will be provided as tablets for oral administration. The 50-mg and 10-mg tablets and their matching placebos will be supplied in blister cards and labeled according to local regulatory requirements. Subjects will receive blinded labeled supplies throughout the study.

In order to achieve the proper dosage and maintain the blind throughout the study, tablets will be dispensed in a blinded fashion to ensure that all subjects, regardless of the assigned treatment sequence, will take the same number of tablets/day. To accomplish this, all subjects will take 7 tablets/day during the loading phase, 4 tablets/day during the maintenance phase, 7 tablets/day during the first 4 weeks of the extension phase, and 4 tablets/day for the remainder of the extension phase.

Statistical Methods:

The study may be unblinded for Sponsor internal decision-making purposes when ≥90% of subjects have reached 24 weeks post-randomization (or discontinued prior to the Week 24 visit), and dissemination of these results will be limited to the unblinded reporting team and Sponsor management. The sponsor personnel who are unblinded will be separate from the study team. The sponsor will still maintain the blind for study team members who will be involved in daily study conduct, study management, safety, and data monitoring through the completion of the study. Investigators and subjects will remain blinded. There will be no impact on B7981015 study conduct, analysis, or reporting.

The sample size for the study was based on the consideration to have sufficient power to evaluate the primary endpoint. A sample size of 120 subjects per group (for the 200 mg/50 mg once daily (QD), 200 mg/30 mg QD, 50 mg/50 mg QD, or 30 mg/30 mg QD groups) will provide more than 90% power to demonstrate that at least the 200 mg/50 mg QD group is superior to placebo by a difference of 24% in the proportion of subjects achieving the primary endpoint (SALT ≤20 at Week 24), assuming a placebo response rate of no more than 5%, at $\alpha = 0.05$ (2-sided significance level). This sample size accounts for multiplicity using a closed testing procedure to ensure strong control of Type I error for all comparisons between active treatment groups and placebo. This sample size additionally provides > 90% power for the SALT ≤ 10 at Week 24 endpoint assuming that the 200 mg/50 mg QD group is superior to placebo by a difference of 20% in the proportion of subjects achieving SALT ≤10, assuming a placebo response rate of no more than 5%, at $\alpha = 0.05$ (2-sided significance level). The assumption of the placebo response rate for both SALT≤20 and SALT≤10, as well as the treatment difference, was informed by the Week 24 results from the Phase 2a Study B7931005.

As noted in Section 9, regulatory requirements for a marketing authorization approval CCI [redacted] will require significance at an α more stringent than 0.05, although the exact level of stringency required may vary (ie, 0.00125 is required by the FDA/PMDA for their requested primary endpoint of SALT ≤20 while 0.01 is required by the EMA for their requested primary endpoint of SALT ≤10). The sample size of 120 subjects per group provide power >90% for SALT ≤20 ($\alpha = 0.00125$) and SALT ≤10 ($\alpha = 0.01$).

The 10 mg/10 mg QD group is included to address the secondary objective of characterizing the exposure response. The sample size of 60 subjects for this group was chosen to allow for estimation of the exposure-response parameters.

For the EMA and competent authorities in the VHP countries, that request that the PGI-C response at Week 24 be analyzed as a key secondary endpoint, a sample size of 120 subjects per group also provides more than 90% power for PGI-C response assuming a difference of 35% and a placebo response rate of 20%, at $\alpha = 0.05$ (2-sided significance level). The assumptions of the treatment difference and placebo response rate for PGI-C response were based on the Concert CTP-543 Phase 2b Study Week 24 data.[90] Under the above assumptions, the power of the study remains >90% at $\alpha = 0.01$ (EMA required 2-sided significance level).

The primary analysis population for efficacy data will be the Full Analysis Set (FAS) defined as all randomized subjects, regardless of whether they received study medication. In the comparison to placebo, the data from the 2 groups, F and G, up to Week 24 will be pooled to form the placebo group.

For the overall study and for the FDA/PMDA, the SALT ≤20 response at Week 24 is the primary endpoint. The SALT ≤10 response at Week 24 will be analyzed as a key secondary endpoint for the overall study but not for the FDA/PMDA. The testing procedures are described in Section 9.2.1.1 and Section 9.2.1.2, and the planned analysis of the primary endpoint are described in Table 6. The primary analysis of the primary endpoint will be

analyzed by Miettinen and Nurminen (MN) method[84] for the difference in the proportion of responders between each active treatment group and placebo. Subjects with missing SALT score at Week 24 due to coronavirus disease 2019 (COVID-19) related reasons will be excluded from the analysis at that timepoint, whereas missing data due to other reasons will be counted as non-responders at that time-point. As supplementary analysis to assess the impact of COVID-19-related missing data on the results of the primary analysis, the analysis of the primary endpoint will be repeated with all missing data considered as non-responders regardless of the reason for missingness.

For the EMA and competent authorities in the VHP countries, the SALT ≤10 response at Week 24 will be the primary endpoint and the PGI-C response at Week 24 will be analyzed as a key secondary endpoint. The testing procedures are described in Section 9.2.1.3, and the planned analyses of the primary endpoint are described in Table 7. The primary analysis of the primary endpoint will be conducted using a generalized linear mixed model (GLMM) model for the longitudinal binary data of SALT ≤10 response over time up to Week 24, assuming a mechanism of missing at random (MAR) for missing data due to COVID-19. Missing data due to reasons not related to COVID-19 will be assumed as non-responders. The key secondary endpoint will also be analyzed using this approach.

To characterize the exposure (dose or average steady state drug concentration [C_{avg}]) response in achieving the primary endpoint, a Bayesian three-parameter maximum effect attributable to the drug (E_{max}) exposure-response model will be used as the primary analysis approach to characterize the exposure response relationship. The response function will be the log odds (logit) of the proportion of subjects achieving the primary endpoint. In modelling the exposure response, the effect of loading dose will be included as a fixed factor in the model. Model-based estimation of treatment effect for each dose or associated C_{avg} compared to placebo will be presented with 95% confidence interval (CI). The model will be described in detail in the Statistical Analysis Plan (SAP).

For secondary endpoints, all binary endpoints will be analyzed in the same way as the primary endpoint for the overall study . For continuous endpoints, a mixed-effect model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, visit, treatment-by-visit interaction, and relevant baseline value when modeling the change from baseline. Within the framework of MMRM, the treatment difference will be tested at each time point.

All secondary endpoints will be evaluated at the 5% level of significance, without adjustments for multiple comparisons.

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

The safety data will be summarized in accordance with Pfizer Data Standards. All subjects who receive investigational product (safety population) will be included in the safety analyses. All safety data will be summarized descriptively.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. If subject visits or procedures are affected by a public emergency, including the coronavirus disease 2019 (COVID-19) pandemic, please refer to Appendix 6.

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

Protocol Activity	**Screening Period**	**Treatment Period**														
		Loading Phase			**Maintenance Phase**				**Extension Phase**					**F/U[b]**	**ET[c]**	
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Visit Day[a]	**Day -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 127**	**Day 169**	**Day 183**	**Day 197**	**Day 239**	**Day 281**	**Day 337**			
Week	**N/A**		**W2**	**W4**	**W8**	**W12**	**W18**	**W24**	**W26**	**W28**	**W34**	**W40**	**W48/EOT**	**EOS**		
Visit Window	**N/A**		**±3 Days based on Day 1 visit**		**±7 Days based on Day 1 visit**				**±3 Days based on Day 1 visit**		**±7 Days based on Day 1 visit**			**+7 Days**		
Enrollment procedure																
Informed consent and if applicable assent	X															
Inclusion/Exclusion criteria	X	X														
Demographics	X															
Medical history and AA disease history[d]	X	X														
Medical procedures																
Complete physical examination[e]	X	X						X					X		X	
Targeted physical examination[f]				X	X	X	X			X	X	X		X		
Vital signs[g]	X	X		X	X	X	X	X		X	X	X	X	X	X	
12-Lead ECG[h]	X	X		X				X		X			X		X	
Height & Weight[i]	X	X						X					X		X	
Chest radiographs[j]	X															
Audiological Evaluation[k]	X							X					X		X	
Laboratory																
Hematology & Serum Chemistry[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting lipid Panel[m]		X		X		X		X		X	X		X	X	X	
Urinalysis[n]	X	X		X	X	X	X	X		X	X	X	X	X	X	
Serum FSH[o]	X															

Protocol Activity	Screening Period	Treatment Period													
		Loading Phase			Maintenance Phase				Extension Phase					F/U[b]	ET[c]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Visit Day[a]	**Day -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 127**	**Day 169**	**Day 183**	**Day 197**	**Day 239**	**Day 281**	**Day 337**		
Week	**N/A**		**W2**	**W4**	**W8**	**W12**	**W18**	**W24**	**W26**	**W28**	**W34**	**W40**	**W48/EOT**	**EOS**	
Visit Window	**N/A**		**±3 Days based on Day 1 visit**		**±7 Days based on Day 1 visit**				**±3 Days based on Day 1 visit**		**±7 Days based on Day 1 visit**			**+7 Days**	
Pregnancy test (WOCBP only)[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV testing[q]	X														
Hep B and Hep C Screening[r]	X														
HBVDNA (applicable countries)[s]	X					X		X			X		X		X
Varicella-zoster virus immunoglobulin G antibody (VZV IgG Ab) (adolescents only, if applicable)[t]	X														
Collection of baseline sample for potential viral screen[u]		X													
Tuberculosis test[v]	X														
Laboratory Pharmacodynamics															
IP-10 (CXCL10)		X		X	X	X		X							
FACS-TBNK		X		X		X		X					X		X
Immunoglobulins (IgA, IgG, IgM)		X						X					X		X
Trial treatment															
Impala registration	X														
Randomization		X													
Investigational product dispensing		X	X	X	X	X	X	X	X	X	X	X			
Investigational product administration[w]		X	→	→	→	→	→	→	→	→	→	→			
Investigational product accountability			X	X	X	X	X	X	X	X	X	X	X		X
Clinical assessments															
SALT	X	X		X	X	X	X	X		X	X	X	X		X
ELA and EBA	X	X		X	X	X	X	X		X	X	X	X		X
Photography[x]	X	X		X		X		X		X		X	X		X
Assessment of Fingernails Affected by AA[y]		X				X		X			X	X	X		X
CGI-AA	X	X		X	X	X	X	X		X	X	X	X		X
C-SSRS[z]	X	X		X		X	X	X		X	X	X	X		X

Protocol Activity	Screening Period	Treatment Period														
		Loading Phase			Maintenance Phase				Extension Phase					F/U[b]	ET[c]	
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Visit Day[a]	**Day -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 127**	**Day 169**	**Day 183**	**Day 197**	**Day 239**	**Day 281**	**Day 337**			
Week	**N/A**		**W2**	**W4**	**W8**	**W12**	**W18**	**W24**	**W26**	**W28**	**W34**	**W40**	**W48/EOT**	**EOS**		
Visit Window	**N/A**		**±3 Days based on Day 1 visit**		**±7 Days based on Day 1 visit**				**±3 Days based on Day 1 visit**		**±7 Days based on Day 1 visit**			**+7 Days**		
Patient reported outcome																
AAPPO		X		X	X	X	X	X			X	X	X		X	
PGI-C and P-Sat				X	X	X	X	X			X	X	X		X	
PHQ-8[z]	X															
HADS		X		X	X	X		X					X		X	
SF36v2 Acute		X		X	X	X		X					X		X	
EQ-5D-5L (adults) or EQ-5D-Y (adolescents)		X		X		X		X					X		X	
AARU		X				X		X			X		X		X	
WPAI: AA (adults only)		X				X		X			X		X		X	
Pharmacokinetic																
Predose PK sampling[aa]		X														
Full PK sampling (including predose sampling)[bb]				X	X	X[bb]										
Banked Biospecimen Collection																
Genomic banked Biospecimen: Prep D1[cc]		X														
Other banked biospecimen: Prep B1		X		X		X		X								
Other banked biospecimen: Prep B2		X		X		X		X								
Other banked biospecimen: Prep R1		X		X		X		X								
Other																
Prior and current concomitant treatment(s) monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contraception check, as applicable	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Check for initiation of menarche (for premenarchal females only)[dd]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Protocol Activity	Screening Period	Treatment Period													
		Loading Phase			Maintenance Phase				Extension Phase					F/U[b]	ET[c]
Visit Identifier	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Visit Day[a]	Day -35 to -1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 127	Day 169	Day 183	Day 197	Day 239	Day 281	Day 337		
Week	N/A		W2	W4	W8	W12	W18	W24	W26	W28	W34	W40	W48/EOT	EOS	
Visit Window	N/A		±3 Days based on Day 1 visit		±7 Days based on Day 1 visit				±3 Days based on Day 1 visit		±7 Days based on Day 1 visit			+7 Days	

Abbreviations: → = ongoing/continuous event; AA = alopecia areata; AAPPO = Alopecia Areata Patient Priority Outcomes; AARU = Alopecia Areata Resource Utilization; CGI-AA = Clinician Global Impression – Alopecia Areata; C-SSRS = Columbia Suicide Severity Rating Scale; CT = Computed Tomography; CXCL-10 = C-X-C motif chemokine 10; EBA = Eyebrow Assessment; ECG = electrocardiogram; ELA = Eyelash Assessment; EOT = End of Treatment; EOS = End of Study; EQ-5D-5L = EuroQoL 5 Dimensions; EQ5D-Y = EuroQoL 5 Dimensions-Youth; ET = Early Termination; FACS-TBNK = fluorescence-activated cell sorting for T-cells, B-cells, and natural killer (NK) cells; FSH = follicle stimulating hormone; F/U = follow-up; HADS = Hospital Anxiety and Depression Scale; HBVDNA = hepatitis B viral DNA; Hep B = hepatitis B; Hep C = hepatitis C; HEENT = head, eyes, ears, nose and throat; HIV = human immunodeficiency virus; Ig = Immunoglobulin; IP10 = Interferon gamma-induced protein 10; MRI = Magnetic Resonance Imaging; N/A = Not Applicable; PGI-C = Patient's Global Impression of Change; PHQ-8 = Patient Health Questionnaire – 8 items; PK = Pharmacokinetic; P-Sat = Patient Satisfaction with Hair Growth; SALT = Severity of Alopecia Tool; SF-36v2 = 36-Item Short Form Health Survey version 2; VZV IgG Ab = varicella-zoster virus immunoglobulin G antibody; WOCBP = women of childbearing potential; WPAI:AA = Work Productivity and Activity Impairment: Alopecia Areata.

a. Day relative to start of study treatment (Day 1).

b. If a subject discontinues from the study for any reason other than death, lost to follow-up, or withdrawal of consent, a Follow-Up Visit must be performed within 28 (+7 days) after the Early Termination visit. In addition, all subjects who complete the study but do not enter the long-term extension study must have a Follow-Up Visit within 28 (+7 days) of End of Treatment visit.

c. For subjects who discontinue early from the study, the procedures scheduled for ET Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. Subject will then require a Follow-Up Visit within 28 (±7) days.

d. Medical history and AA disease history includes detailed histories of conditions specified in Study Procedures Section 6.1.

e. Complete physical examination consists of general appearance, skin, head, eyes, ears, nose and throat (HEENT); mouth, heart, lungs, abdomen, extremities, neurologic function, back, and lymph nodes. In addition, dermatological full body exam must be performed. Dermatological examinations should include visual inspection of the breasts and external genitalia. When dermatologic adverse events are identified on physical exam, additional procedures may be required. Please refer to Section 7.5.6.2 for additional details.

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

g. Vital signs, including pulse rate, blood pressure, respiratory rate, and temperature (eg, oral, tympanic, or axillary), should be performed before ECG and laboratory blood collection as specified in the protocol.

h. ECG should be performed before laboratory blood collection.

i. Height and weight will be measured without shoes or outerwear.

Protocol Activity	Screening Period	Treatment Period														
		Loading Phase			Maintenance Phase				Extension Phase					F/U[b]	ET[c]	
Visit Identifier	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Visit Day[a]	Day -35 to -1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 127	Day 169	Day 183	Day 197	Day 239	Day 281	Day 337			
Week	N/A		W2	W4	W8	W12	W18	W24	W26	W28	W34	W40	W48/EOT	EOS		
Visit Window	N/A		±3 Days based on Day 1 visit		±7 Days based on Day 1 visit				±3 Days based on Day 1 visit		±7 Days based on Day 1 visit			+7 Days		

j. Chest X-ray or other appropriate diagnostic imaging (ie, CT or MRI) should be performed at Screening (unless taken within 3 months prior to the Screening visit). Chest X-rays are required and should be performed as per local guidelines and standard of care (eg, posterior-anterior and lateral views). Official reading must be located in the source documentation.

k. For Screening, the audiological evaluation may be performed within 8 weeks prior to Day 1 but results must be available prior to Day 1 in order to assess eligibility. At Screening, this includes audiological history, otoscopic examination, pure tone audiometry, air and bone conduction, speech audiometry, and immittance audiometry. At subsequent visits, updated audiological history, otoscopic examination, and pure tone audiometry will be performed; based upon results, additional audiometry assessments may be required. For details, refer to the Audiometry Study Guide. All procedures must be performed as per the Audiometry Study Guide. For subjects who terminate early from the study, efforts must be made to complete the audiological evaluation.

l. Hematology includes hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count, total neutrophils (%, Abs), basophils (%, Abs), eosinophils (%, Abs), lymphocytes (%, Abs), monocytes (%, Abs), and reticulocyte count (%, Abs). Serum chemistry includes BUN/urea, 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, and creatine kinase. At Weeks 2 and 26, only hematology will be performed.

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

n. Urinalysis will be performed by the central laboratory. Microscopic analysis will be performed if urinalysis is positive for blood, nitrite, leukocyte esterase, and/or protein. Urine culture will be performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.

o. Follicle stimulating hormone (FSH) test must be performed at Screening to confirm postmenopausal status in female subjects under 60 years old and who have been amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause to confirm postmenopausal status.

p. Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential. In the event that urine pregnancy tests are not permitted at an institution, serum pregnancy tests can be utilized. In addition to urine pregnancy tests performed at each study visit, sites in Voluntary Harmonisation Procedure (VHP) countries in the European Medicines Agency (EMA) should instruct female subjects of childbearing potential to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44). In addition, the investigator or designee will instruct the subject to contact the site immediately if the urine pregnancy test result is positive or cannot be confirmed as negative. The VHP countries participating in this study are Czech Republic, Germany, Hungary, Poland, and Spain.

q. Subjects who are positive for HIV antibodies will be screen-failed.

r. All subjects will undergo Screening for Hep B and Hep C for eligibility. All subjects will undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Subjects who are HBsAg positive will not be eligible for this study. Subjects who are HBsAg negative but HBcAb positive will be reflex-tested for hepatitis B surface antibody (HBsAb). Additional reflex testing for hepatitis B virus DNA testing (HBVDNA) is also required for HBcAb positive subjects in countries in which Hep B prevalence has been reported at a rate of >5.0% or if required by local standard of care.

Protocol Activity	Screening Period	Treatment Period														
		Loading Phase			Maintenance Phase				Extension Phase					F/U[b]	ET[c]	
Visit Identifier	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Visit Day[a]	Day -35 to -1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 127	Day 169	Day 183	Day 197	Day 239	Day 281	Day 337			
Week	N/A		W2	W4	W8	W12	W18	W24	W26	W28	W34	W40	W48/EOT	EOS		
Visit Window	N/A		±3 Days based on Day 1 visit		±7 Days based on Day 1 visit				±3 Days based on Day 1 visit		±7 Days based on Day 1 visit			+7 Days		

Please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria. For Japan-specific requirements, see Appendix 5.1. For all subjects in the study, Hep C testing will be performed using hepatitis C antibody. Subjects who are HCVAb positive will be reflex-tested for HCV RNA. Subjects who are positive for HCVAb and HCV RNA will not be eligible for this study.

s. HBVDNA testing will be performed at Weeks 12, 24, 34, 48, and Early Termination for subjects who were enrolled with a positive HBcAb and a negative HBVDNA in those regions for which Hep B prevalence has been reported at a rate of >5.0% or if required by local standard of care (refer to Section 7.5.11 for information regarding which screening laboratory results should be used to determine whether HBVDNA testing should be performed). Testing at additional time points may be performed as per the local standard of care. For Japan-specific requirements see Appendix 5.1. For all other countries, please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria.

t. Varicella-zoster virus immunoglobulin G antibody (VZV IgG Ab) testing is required to confirm eligibility only in adolescent subjects who have no documented evidence of having received varicella vaccination (2 doses).

u. A serum sample will be collected at baseline and submitted to the central lab. The sample will be stored and analyzed at a later date only at the sponsor's request. For example, 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 subject had exposure to that virus.

v. A documented TB test performed within 12 weeks prior to Day 1 is acceptable. Subjects with a history of tuberculosis may not require TB testing as per the protocol exclusion criteria in Section 4.2 Exclusion Criterion 21. Perform TB test procedure using the QuantiFERON®-TB Gold In Tube (QFT-G) test. If QFT-G test is not available, the T-SPOT®.*TB* (T-Spot) test can be used. A negative Purified Protein Derivative (PPD) test can be substituted for the QFT-G test or T-Spot test only under specific circumstances described in Section 7.5.8.

w. Dosing instructions will be provided to the subject and reviewed by the site at each visit. Subjects should be encouraged to take the medication in the morning whenever possible. Subjects should take the medication at approximately the same time every day. However, at study visit days, subjects are to be instructed to refrain from dosing at home and are to take the dose in the clinic.

x. Scalp photographs will be obtained at Screening to verify eligibility. Scalp areas photographed should be recorded in study documents so that the same scalp region(s) is (are) photographed at all time points as applicable. Photographs of eyelashes and eyebrows will also be taken.

y. The number of fingernails affected by AA will be counted.

z. Subjects who have recent or active suicidal ideation or behavior will be excluded from the study. For specific criteria regarding subjects with prior suicidal ideation or behavior, see Section 4.2.

aa. Only predose blood sample for PK will be collected at baseline (Visit 2 Day 1).

Protocol Activity	Screening Period	Treatment Period													
		Loading Phase			Maintenance Phase				Extension Phase					F/U[b]	ET[c]
Visit Identifier	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Visit Day[a]	Day -35 to -1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 127	Day 169	Day 183	Day 197	Day 239	Day 281	Day 337		
Week	N/A		W2	W4	W8	W12	W18	W24	W26	W28	W34	W40	W48/EOT	EOS	
Visit Window	N/A		±3 Days based on Day 1 visit		±7 Days based on Day 1 visit				±3 Days based on Day 1 visit		±7 Days based on Day 1 visit			+7 Days	

bb. Blood samples for PK will be collected at predose and postdose 0.5 hr, 1 hr and 3 hr at Week 4; blood samples will be collected for predose and postdose 0.5 hr and 2 hr at Week 8. For each blood sample collection, the allowable windows are as follows for time postdose: 0.5 hr (±10 min), 1 hr (±15 min), 2 hr (±20 min) and 3 hr (±30 min). If the blood samples for PK were collected at Week 8, no PK samples are required at Week 12.

cc. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

dd. In female subjects who are premenarchal at the start of the study, the investigator must confirm with the subject at every visit whether menarche has started since the last visit. If menarche has started, the subject must now be considered of childbearing potential; therefore, from that point forward, the subject must be required to use contraception as described in Section 4.3.1 and to undergo contraception checks and pregnancy testing according to the Schedule of Activities, starting with the current visit. In addition, the investigator or designee must instruct the subject to call the study site immediately if the subject begins menarche between study visits.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06651600 is an orally bioavailable, small molecule that is currently being investigated in patients with alopecia areata (AA). PF-06651600 inhibits, by irreversibly blocking the adenosine triphosphate (ATP) binding site, JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family (BTK, BMX, ITK, TEC, TXK), with high selectivity over the other three JAK isoforms, JAK1, JAK2, and tyrosine kinase 2 (TYK2), as well as over the broader kinome. PF-06651600 potently inhibits signaling of the common gamma (γ)-chain receptors for interleukin (IL)-15 and IL-21, which have been implicated in the pathogenic pathways of AA.[1] Additionally, PF-06651600 inhibits the cytotoxic function of $CD8^+$ T cells and natural killer (NK) cells which have also been implicated in the pathogenic process of AA.[2,3] This inhibition may be mediated through mechanisms dependent on JAK3 and TEC kinase family members.[4,5,6]

1.2. Background and Rationale

1.2.1. Background on Alopecia Areata

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

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

Clinical presentation of AA can be limited to small, circular patches of scalp hair loss (patchy hair loss, alopecia focalis), involve complete loss of hair on the scalp (alopecia totalis [AT]), or total loss of hair on the scalp and body (alopecia universalis [AU]).[12] AA involving 50% or greater scalp hair loss, including AT and AU, is considered an advanced form of alopecia, according to the United States (US) National Alopecia Areata Foundation.[13] 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.[15] It is estimated that AA affects as many as 6 to 7 million individuals in the US[8] and 147 million worldwide.[13]

The spontaneous remission rates for AA patients presenting with <50% scalp hair loss (patchy hair loss, alopecia focalis) are 30-50% within the first 6-12 months of disease onset, and 66% of the patients will show complete regrowth of hair within 5 years.[14] The likelihood of complete regrowth spontaneously with AT or AU is less than 10%.[16]

Further, there is evidence that AA can become refractory to JAK inhibition if it has been present for a substantial period of time. Specifically, a recent case series demonstrated that AA patients whose current episode of alopecia totalis or alopecia universalis had lasted more than 10 years were highly non-responsive to off-label tofacitinib treatment in comparison with patients with shorter duration.[17]

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.[19,20] 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,[21-,25] problems with social relations,[26] decreased health-related quality of life (HRQoL) and general quality of life (QoL), as well as the QoL of their families.[27-35]

AA is a disease with significant pediatric prevalence, in addition to the burden of disease seen in adults, and ample evidence is available on the impact of AA on the mental health of adolescent patients. In a US study, children with AA had more psychological problems than those without AA. Specifically, those with AA exhibited more anxiety, depression, tendencies to withdraw, aggression, and delinquency. In addition, children with AA were more likely to exhibit somatic problems as well as problems in social relations and in attention span. Girls with AA seem to have been affected more in dimensions of total problems, anxiety/depression, and internalizing/externalizing syndromes. Children with AA were also less likely to have experienced positive life events in the year prior to exhibiting AA symptoms.[26]

In addition to experiencing a significant mental health burden, children with AA report experiencing other negative impacts to their QoL. Specifically, 75% of children aged 15-19 years reported instances of effects on QoL, 50% reported that the disease limited their participation in activities, 40% reported instances of bullying, and 35% reported that others noticed and commented on their condition. Rates of decrement in QoL, limitations on participation in activities, and bullying were heightened in older children aged 15-19 years compared to younger children.[36]

Given the finding that complete scalp hair loss with duration >10 years in adults is less likely to respond to treatment, pursuing treatment, even if only intermittently, in adolescents or even younger patients with stable, severe AA may prevent future irreversible hair loss.[17] Additionally, an earlier age of first onset has been reported to correspond to an increased lifetime risk of extensive disease. Differences in treatment responses are not expected for adolescent versus adult AA patients as suggested in 2 reports of tofacitinib (off-label use).[17,37]

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. However, there is neither a cure for AA, nor is there a therapy convincingly demonstrated to induce and sustain remission long term.[38-42]

1.2.2. Drug Development Rationale

The JAK family, including JAK1, JAK2, JAK3 and TYK2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function.[43,44] Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducer and activator of transcription (STAT) family of transcription factors. The STATs are phosphorylated and subsequently translocate to the nucleus where they bind to specific gene promoters to activate transcription of a range of target genes.[43,44]

JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including IL-2, IL-4, IL-5, IL-6, IL-12, IL-13, IL-15, IL-21, IL-23, IL-31, IFNα, and IFNγ.[43]

The cytokine signaling pathways of IFNγ and IL-15, among others, can be blocked via JAK inhibition, supporting the rationale of a JAK inhibitor in the treatment of AA.[45] Treatment with the JAK inhibitors tofacitinib and ruxolitinib are reported to reverse AA in a mouse model.[2] Clinically, there are case reports and case series reporting that these JAK inhibitors demonstrate efficacy in AA.[2,17,18,46-51]

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

1.3. Nonclinical and Phase 1 Efficacy and Safety Data

Data from nonclinical and Phase 1 programs supports the planned clinical trials with PF-06651600.

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

Further information is available in the current version of the Investigator's Brochure (IB).

The potential for PF-06651600 to be involved in drug-drug interaction (DDI) is being investigated. If results exclude a clinically meaningful DDI (eg, relative to AUC) between PF-06651600 and a perpetrator or victim drug then that perpetrator or victim drug will no longer be prohibited as a concomitant medication; this information will be communicated via an administrative letter. Refer to Section 5.8.2 for medications prohibited to be used prior to and during the study.

1.4. Clinical Experience

There are complete and ongoing Phase 2 and 3 studies with PF-06651600 in a number of disease indications. Forty-two (42) patients with rheumatoid arthritis were exposed to PF-06651600 in the Phase 2a study B7981006.[91] Forty-eight (48) subjects were exposed to PF-06651600 in the Phase 2a Alopecia Areata study B7931005 in the initial 24-week period.[92] There are ongoing studies in subjects with ulcerative colitis (B7981005)[93], Crohn's disease (B7981007)[94], and vitiligo (B7981019)[95]. These studies are expected to expose approximately 180, 125, and 330, respectively, to once daily (QD) PF-06651600 treatment. The duration of exposure will range from 24 to 32 weeks in B7981005, from 52 to 64 weeks in B7981007, and up to 48 weeks in B7981019. In addition, there is the B7981032 study, an ongoing Phase 3 open-label study for subjects with alopecia areata who have previously enrolled in either the B7931005 or B7981015 studies as well as de novo subjects who have not received study intervention in either of those studies.[96] Approximately 450 de novo subjects and 510 subjects from B7931005 or B7981015 will be exposed to PF-06651600 in the B7981032 study and the duration of exposure will range up to 26 months.

1.4.1. Phase 2a Study in Alopecia

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

During the initial 24-week treatment period, subjects were treated with 200 mg QD during a 4-week induction phase followed by dosing with 50 mg QD in a maintenance phase in the PF-06651600 group. The primary efficacy endpoint in the study was mean change from baseline in SALT score at Week 24. At Week 24, analysis provided data on both efficacy and safety, and indicated clinical improvement for subjects treated with PF-06651600. PF-06651600 met the predefined primary decision criterion (mean change from baseline [CFB] in SALT score, adjusted p-value <0.025, and point estimate >20% at Week 24). The Mixed effect Model Repeat Measurement (MMRM) estimates for PF-06651600 compared to placebo at Week 24 for SALT mean CFB (95% CI) were 33.6 [95% CI= (21.4, 45.7); Hochberg p (1-sided) <0.0001]. PF-06651600 differentiates from placebo (statistically significant), as early as Week 6. Overall, the placebo response was almost negligible. PF-06651600 also differentiates from placebo on the proportion of responders in eyelash assessment (ELA) and eyebrow assessment (EBA).

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

infections. The majority of events were mild. No serious infections, malignancies, cases of herpes zoster, or cases of herpes simplex were reported in the PF-06651600 group. Hematological changes were observed in both active groups during the induction and maintenance periods but were not associated with clinically relevant TEAEs. During the induction period, when subjects received PF-06651600 200 mg QD for 4 weeks, decreases in mean platelet and lymphocyte counts (-18% and -24% mean CFB, respectively) were observed in the PF-06651600 group. During the maintenance period, when subjects received 50 mg QD for 20 weeks, there was improvement in the platelet and lymphocyte counts in the PF-06651600 group. Neutrophil counts were increased at Week 4 (12% CFB) and Week 24 (10% CFB) in the PF-06651600 treatment group. Two subjects in the PF-06651600 group discontinued due to TEAEs.

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

1.4.2. 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 subjects with moderate-to-severe active rheumatoid arthritis (RA) with an inadequate response to methotrexate. A total of 70 subjects were randomized to study treatment; 28 subjects received placebo and 42 subjects received PF-06651600 (200 mg QD).

PF-06651600 was determined to be generally safe and well tolerated in this study. There were no deaths or SAEs. TEAEs were numerically higher in subjects receiving PF-06651600 compared to those receiving placebo. The TEAEs reported in more than 5% subjects with RA receiving PF-06651600 were influenza and lymphopenia. The majority of the TEAEs were mild in severity. There was 1 mild case of herpes simplex in the PF-06651600 group that was considered to be treatment-related with no cases in the placebo group. There were no clinically relevant changes in vital signs, electrocardiogram (ECG), or audiometric assessments. By the Week 8 time point (as early as 2 weeks), in the PF-06651600 group, there were decreases in the median platelet counts (25% change from baseline), lymphocyte counts (21% change from baseline), neutrophil counts (24% change from baseline), and hemoglobin (3% change from baseline). None of these were deemed to be clinically relevant by the investigator and values returned to near baseline by the 12-week follow-up visit.

1.4.3. Clinical Pharmacokinetics and Metabolism

Pharmacokinetics, bioavailability, and food effect have been studied in several Phase 1 clinical trials. For a complete description of these studies, please refer to the IB.

These studies demonstrated that the PK profile of PF-06651600 is characterized by rapid absorption with time (T_{max}) to first occurrence of maximum plasma concentration (C_{max}) values <1 hour and rapid elimination (half-life [$t_{½}$] of 1.1–2.5 hours). Systemic exposures increase in an approximately dose proportional manner across 50 mg to 400 mg total daily dose with observed accumulation ratios (R_{ac}) ranging from 1-1.8. A similar PK profile was observed in Japanese subjects following administration of 200 mg PF-06651600 QD for 10 days. The bioavailability of a solid dose formulation of PF-06651600 relative to a

solution formulation under fasting conditions and the effect of food on the bioavailability of the solid dosage formulation of PF-06651600 was evaluated. The relative bioavailability of the PF-06651600 tablet as measured by area under the plasma concentration time curve from time zero to infinity (AUC_{inf}) is similar to that of an oral solution. PF-06651600 can be administered with or without food.

In vitro and in vivo metabolite profiling suggested that the primary clearance mechanisms for PF-06651600 were glutathione-related conjugation and cytochrome P450 (CYP)-mediated oxidation with the major contributing isoform being CYP3A4. No unique human metabolites were observed clinically compared to metabolite profiles in mouse, rat, and dog. PF-06651600 showed a low risk of inhibition and induction of the major CYP450 and uridine diphosphate glucuronosyltransferase (UGT) enzymes, although time-dependent inhibition of CYP1A2 (inhibitory concentration 50% [IC_{50}] = 65 µM) and CYP3A4/5 (IC_{50} = 11 to 14 µM) was observed. PF-06651600 showed a low potential to inhibit organic anion transporting polypeptide (OATP) 1B1, OATP1B3, bile salt export pump (BSEP), organic cation transporter (OCT)2, organic anion transporter (OAT)1, and OAT3 at clinically relative concentrations. However, PF-06651600 has the potential to inhibit P-glycoprotein (P-gp) (systemically and in the gastrointestinal [GI] tract), breast cancer resistance protein (BCRP) (systemically and in the GI tract), OCT1, multidrug and toxin extrusion (MATE)1, and MATE2K at clinically relevant concentrations.

In general, systemic exposures in the adolescent populations do not differ significantly from adults, which justifies similar doses for adults and adolescents.[52,53] Based on the current knowledge of the disposition of PF-06651600, which is primarily metabolism, adolescents are expected to have a similar range of exposures as seen in adults.

1.5. Study Rationale

This study is being conducted to evaluate the efficacy and safety of multiple doses/regimens of PF-06651600 in comparison with placebo over the first 24 weeks treatment duration. This will be followed by an additional 24-week extension period during which all subjects will receive active treatment including those subjects who received placebo during the initial 24 weeks of the study.

This study will test multiple dose regimens, including the dose regimen with demonstrated clinical efficacy in the ongoing Phase 2a Study B7931005[92], as well as several lower doses to evaluate dose-response relationships. The rationale for selection of the dosing regimens in this study is further described in Section 1.6.

In addition to dose-ranging, the other objectives of this study are to support registration for treatment of patients with moderate to severe AA and to evaluate safety in this population. To achieve this, response based on absolute SALT score ≤20 at Week 24 will be the primary endpoint for analyzing a dose-response and for confirming a clinically meaningful treatment effect in patients with AA.[89] SALT is an instrument that is widely used to assess severity of AA by visual determination of the amount of terminal hair loss and summing across four views of the scalp (left side, right side, top and back; range 0-100%).[54,55] This tool has been well accepted and used in multiple AA clinical trials (NCT02691117; NCT01950780; and NCT01797432) as a reliable and reproducible measure of disease severity.[17,18,49,56]

The extension phase of this study will provide additional blinded safety and efficacy data, including long-term data in subjects initially randomized to active treatment as well as data in subjects initially randomized to placebo and subsequently advanced to active treatment at Week 24.

The total sample size for the study is approximately 660 randomized subjects.

1.6. Dose Rationale

This study will evaluate PF-06651600 administered at a loading dose of 200 mg QD for 4 weeks followed by maintenance doses of 30 mg and 50 mg QD for 20 weeks relative to placebo (until the primary endpoint, Week 24). The maintenance doses will then be continued for an additional 24 weeks. Additionally, doses of 10 mg, 30 mg and 50 mg QD will be evaluated relative to placebo for 24 weeks and continued for an additional 24 weeks as a fixed-dose regimen (ie, without loading dose).

The rationale for the selection of the doses and regimens is based on:

- Efficacy and safety results for the initial 24 weeks of PF-06651600 treatment from Study B7931005[92] in subjects with AA.
- Dose/Exposure response relationships observed for PF-06651600 relevant biomarkers.
- Safety results for PF-06651600 from Study B7981006[91] in subjects with RA.
- Exposure margins of proposed clinical doses relative to nonclinical no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) exposures (Table 1).

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

Mechanistically, PF-06651600 inhibits signaling of the common-γ chain receptors for IL-15 and IL-21, which have been implicated in the pathogenic pathways of AA. There is also evidence of modulation of IP-10, which is a marker related to IFNγ.

The need for a loading-dose regimen is based on the hypothesis that maximal inhibition of the relevant immunomodulatory pathways at initiation of treatment can accelerate clinical response which can be maintained by the subsequent lower maintenance dose. The 200 mg dose chosen as the loading dose is expected to produce a >70% IL-15 and IL-21 in vitro signaling inhibition, with ~40% reduction in IP-10 levels from baseline. The 200 mg dose has demonstrated acceptable safety over 4 weeks in B7931005 in AA patients and 8 weeks in B7981006 in moderate to severe RA patients as described in Section 1.4.

The highest maintenance dose of 50 mg is expected to produce ~30-40% IL-15 and IL-21 in vitro signaling inhibition, with ~18% reduction in IP-10 levels from baseline. The 50 mg maintenance dose demonstrated acceptable safety over a 20-week period in Study B7931005 in AA patients as described in Section 1.4.1.

Exposure margins of the proposed clinical doses relative to the NOAEL exposures are summarized in Table 1.

The dose of 10 mg is likely to be a minimally efficacious dose as it is expected to produce a <10% change from baseline in IP-10 levels.

In this study, PF-06651600 doses of 10 mg, 30 mg, and 50 mg will be evaluated as a fixed regimen, and 30 mg and 50 mg will also be evaluated following the 200 mg loading dose, in order to identify the optimal clinical dose and regimen necessary.

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 (B7931005)				
Dog 2-month toxicology (Study 1)	NOAEL: 45 mg/kg oral	44100	5464	8.1
Dog 9-month toxicology (Study 2)	NOAEL: 10 mg/kg oral	7940	5464	1.5
Safety Exposure Margins for 50 mg QD Dose (B7931005)				
Dog 2-month toxicology (Study 1)	NOAEL: 45 mg/kg oral	44100	1213	36
Dog 9-month toxicology (Study 2)	NOAEL: 10 mg/kg oral	7940	1213	6.5

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

1.7. Summary of Benefit/Risk Assessment

In the Phase 2a proof-of-concept Study B7931005[92] in adult patients with AA, PF-06651600 met its primary endpoint of improvement in SALT score relative to placebo at Week 24. PF-06651600 appeared generally safe and well tolerated as suggested by adverse event (AE) number and profile. Reductions in platelet counts and lymphocyte counts were observed during treatment with 200 mg QD but were not considered clinically meaningful and improved after switching to 50 mg QD during the maintenance phase of the study. PF-06651600 is an immunomodulator and, as such, can be associated with the potential risk of infection (including serious infection), opportunistic infections, and viral reactivation. The risk of infection will be monitored and evaluated in longer term studies of PF-06651600.

These preliminary clinical data indicate that PF-06651600 has a favorable benefit: risk profile and provides meaningful clinical benefit in a serious disease with no approved treatment options. The benefit of evaluating PF-06651600 in adolescents is additionally supported by prevalence of AA in adolescents, the significant psychological burden of disease in this population, and a recent case series suggesting that extended duration of AA appears to increase likelihood of being refractory to off-label tofacitinib treatment.

It is not known whether PF-06651600 is secreted into human milk. In animals, PF-06651600 was associated with fetal changes in bones and some internal organs, and lower fetal body weights. Because of the investigational nature of PF-06651600, it should not be administered to pregnant women, breastfeeding women, or fertile women of childbearing potential who are unwilling or unable to use contraception as defined in the study protocol. PF-06651600 is not likely to transfer to a partner through semen at pharmacologically relevant levels.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

1.8. Additional Information

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on AA.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

The following table details the overall study objectives and endpoints. There are some region specific differences noted throughout. Table 5 in Section 9 lists the primary and secondary endpoints of the study organized by known regional requirements.

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 compared to placebo in adult and adolescent alopecia areata (AA) subjects with 50% or greater scalp hair loss on regrowth of lost hair (measured by an absolute Severity of Alopecia Tool (SALT) Score ≤20) at week 24. Note: For the European Medicines Agency (EMA) and competent authorities in the Voluntary Harmonisation Procedure (VHP) countries,[a] the primary objective is to evaluate the efficacy of PF-06651600 compared to placebo in adult and adolescent AA subjects with 50% or greater scalp hair loss on regrowth of lost hair (measured by an absolute Severity of Alopecia Tool (SALT) Score ≤10) at Week 24.	• Response based on an absolute Severity of Alopecia Tool (SALT) Score ≤20 at Week 24. Note: For the EMA and competent authorities in the VHP countries, response based on an absolute SALT Score ≤10 at Week 24 will be analyzed as the primary endpoint in a separate analysis.
Key Secondary Objective(s)	**Key Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 compared to placebo in adult and adolescent AA subjects with 50% or greater scalp hair loss on regrowth of lost hair (as measured by an absolute SALT Score ≤10) at Week 24. Note: This key secondary objective will be utilized as the primary objective for the EMA and competent authorities in the VHP countries. Additionally, this key secondary objective will not apply for the United States Food and Drug Administration (FDA)/Japan Pharmaceuticals and Medical Devices Agency (PMDA).	• Response based on an absolute SALT Score ≤10 at Week 24. Note: This key secondary endpoint will be utilized as the primary endpoint for the EMA and competent authorities in the VHP countries. Additionally, this key secondary endpoint will not apply for the FDA/PMDA.
• To evaluate the effect of PF-06651600 on patient centered outcomes (as measured by PGI-C response) at Week 24. Note: This key secondary objective is only applicable for the EMA and competent authorities in the VHP countries.	• PGI-C response defined as a score of "moderately improved" or "greatly improved" at Week 24. Note: This key secondary endpoint is only applicable for the EMA and competent authorities in the VHP countries.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To characterize the exposure response of PF-06651600 on regrowth of lost hair.	• Response based on an absolute SALT Score ≤20 at Week 24 will be used to characterize the exposure response.[b]
• To assess the efficacy of PF-06651600 on regrowth of lost hair during the treatment period over time.	• Response based on an absolute SALT score ≤20 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48.[c,d]

	• Response based on an absolute SALT score of ≤10 at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.[e] • Response based on a 75% improvement in SALT score from baseline (SALT75) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Change from baseline in SALT scores at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Response based on at least a 2-grade improvement or a score of 3 in Eyebrow Assessment (EBA) score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Response based on at least a 2-grade improvement or a score of 3 in Eyelash Assessment (ELA) score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate the effect of PF-06651600 on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.[f]	• PGI-C response defined as a PGI-C score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.[f] • Change from baseline in Alopecia Areata Patient Priority Outcomes (AAPPO) scales at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.
• **Safety Objective(s)**	**Safety Endpoint(s)**
• To evaluate the safety and tolerability of PF-06651600 in the treatment period over time.	• Incidence of treatment-emergent adverse events (AEs). • Incidence of serious AEs (SAEs) and AEs leading to discontinuation. • The incidence of clinically significant abnormalities in vital signs. • The incidence of clinically significant abnormalities in clinical laboratory values.
• **PK Objective(s)**	**PK Endpoint(s)**
• To characterize pharmacokinetics of PF-06651600.	• Plasma concentrations of PF-06651600 at Weeks 4, and 8 or 12.
Exploratory Objective(s):	**Exploratory Endpoint(s):**
• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.
• To assess the efficacy of PF-06651600 on regrowth of lost hair during the treatment period over time.	• Response based on a 50% improvement in SALT score from baseline (SALT50) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Absolute SALT scores at Baseline, Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.

• To evaluate the effect of PF-06651600 on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.	• Improvement on PGI-C defined as "slightly improved", "moderately improved", or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48. • Improvement on Patient Satisfaction with Hair Growth (P-Sat) items defined as slightly, moderately, or very satisfied at Weeks 4, 8, 12, 18, 24, 34, 40, and 48. • Change from baseline in EuroQoL 5 Dimensions (EQ-5D-5L) in adults or EuroQoL 5 Dimensions-Youth (EQ-5D-Y) in adolescents at Weeks 4, 12, 24, and 48. • Change from baseline in Alopecia Areata Resource Utilization (AARU) at Weeks 12, 24, 34, and 48. • Change from baseline in Work Productivity and Activity Impairment: Alopecia Areata (WPAI:AA) at Weeks 12, 24, 34, and 48. • Change from baseline in the depression subscale score of the Hospital Anxiety and Depression Scale (HADS) at Weeks 4, 8, 12, 24, and 48.[g,87] • Change from baseline in the anxiety subscale score of the HADS at Weeks 4, 8, 12, 24, and 48.[g,87] • Improvement on HADS among subjects with a baseline subscale score indicative of depression who achieved a "normal' subscale score indicative of an absence of depression at Weeks 4, 8, 12, 24, and 48.[g,79,88] • Improvement on HADS among subjects with a baseline subscale score indicative of anxiety who achieved a "normal' subscale score indicative of an absence of anxiety at Weeks 4, 8, 12, 24, and 48.[g,79,88] • Change from baseline in 36-Item Short Form Health Survey version 2 Acute (SF36v2 Acute) at Weeks 4, 8, 12, 24, and 48.
• To evaluate the effect of PF-06651600 on the clinician global impression of severity of scalp hair loss.	• Change from baseline in Clinician Global Impression – Alopecia Areata (CGI-AA) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate efficacy of PF-06651600 in AA nail disease over time.	• Change from baseline in fingernails affected by AA at Weeks 12, 24, 34, 40, and 48.
• To assess pharmacodynamic and disease-related biomarkers over time.	• Change from baseline in interferon gamma-induced protein 10 (IP-10) at Weeks 4, 8, 12, and 24.

	• Change from baseline in percent and absolute lymphocyte subsets (T-cell, B-cell, and natural killer [NK] cells) at Weeks 4, 12, 24, and 48. • Change from baseline in immunoglobulins (IgA, IgG, IgM) at Weeks 24 and 48.

a. The VHP countries participating in this study are Czech Republic, Germany, Hungary, Poland, and Spain.
b. For the EMA and competent authorities in the VHP countries, when SALT ≤10 is utilized for the primary endpoint, exposure response will be analyzed utilizing SALT ≤10 in a separate analysis.
c. For the EMA and competent authorities in the VHP countries, when SALT ≤10 is utilized for the primary endpoint, SALT ≤20 at Week 24 will be analyzed as a secondary endpoint.
d. When SALT ≤20 response at Week 24 is utilized as the primary endpoint, responses based on absolute SALT score ≤20 at Weeks 18, 12, 8 and 4 will be analyzed controlling for Type I error utilizing an appropriate testing procedure. When SALT ≤10 response at Week 24 is utilized as the primary endpoint, the response based on absolute SALT score ≤20 at Week 24 will be analyzed controlling for Type I error utilizing an appropriate testing procedure.
e. When SALT ≤20 response at Week 24 is utilized as the primary endpoint, the response based on absolute SALT score ≤10 at Week 24 will be analyzed controlling for Type I error utilizing an appropriate testing procedure. When SALT ≤10 response at Week 24 is utilized as the primary endpoint, the responses based on absolute SALT score ≤10 at Weeks 18, 12, 8 and 4 will be analyzed controlling for Type I error utilizing an appropriate testing procedure.
f. For the EMA and competent authorities in the VHP countries, the evaluation of the effect of PF-06651600 on patient centered outcomes (as measured by PGI-C response at Week 24) is a key secondary objective. The PGI-C response at Week 24 will be analyzed as a key secondary endpoint utilizing an appropriate testing procedure to control overall Type I error.
g. For the EMA and competent authorities in the VHP countries, endpoints utilizing the HADS will be analyzed as secondary endpoints.

3. STUDY DESIGN

Study B7981015 will investigate PF-06651600 in subjects with moderate to severe AA. This is a Phase 2b/3, randomized, double-blind, placebo-controlled, dose-ranging study. The study will have a maximum duration of approximately 57 weeks. This includes an up to 5-week Screening period, a 48-week treatment period, and a 4-week follow-up period as shown in Figure 1. The treatment period will be comprised of a placebo-controlled period that includes a 4-week loading phase and a 20-week maintenance phase, followed by a 24-week extension phase. The study will enroll a total of approximately 660 subjects. The study will be conducted at approximately 120 sites.

To be eligible to enroll in this study, subjects must have moderate to severe AA with ≥50% hair loss of the scalp (SALT score ≥50) at both Screening and baseline visits, without evidence of terminal hair regrowth within the previous 6 months and with the current episode of hair loss ≤10 years. The full list of eligibility criteria for the study is included in Section 4.

Screening will occur within 35 days prior to the first dose of study drug to confirm that subjects meet selection criteria for the study. Photographs will be taken at the Screening Visit to verify eligibility (AA with ≥50% hair loss of the scalp). Eligible subjects will be randomized as described below.

A stratified randomization will be used for operational purposes in order to achieve a target global composition for AT/AU and adolescent subjects in the enrolled population. The targets for enrollment are approximately 40% AT/AU and approximately 15% adolescents.

The randomization will be operationalized as follows. In regions enrolling both adolescents and adults, there will be four strata:

<18 years of age and AT/AU;

<18 years of age and not AT/AU;

≥18 years of age and AT/AU; and

≥18 years of age and not AT/AU.

Within each of these strata, subjects will be randomized in a 2:2:2:2:1:1:1 manner to blinded PF-06651600 and matching placebo for a total of 7 treatment sequences.

In regions enrolling only adults, there will be two strata:

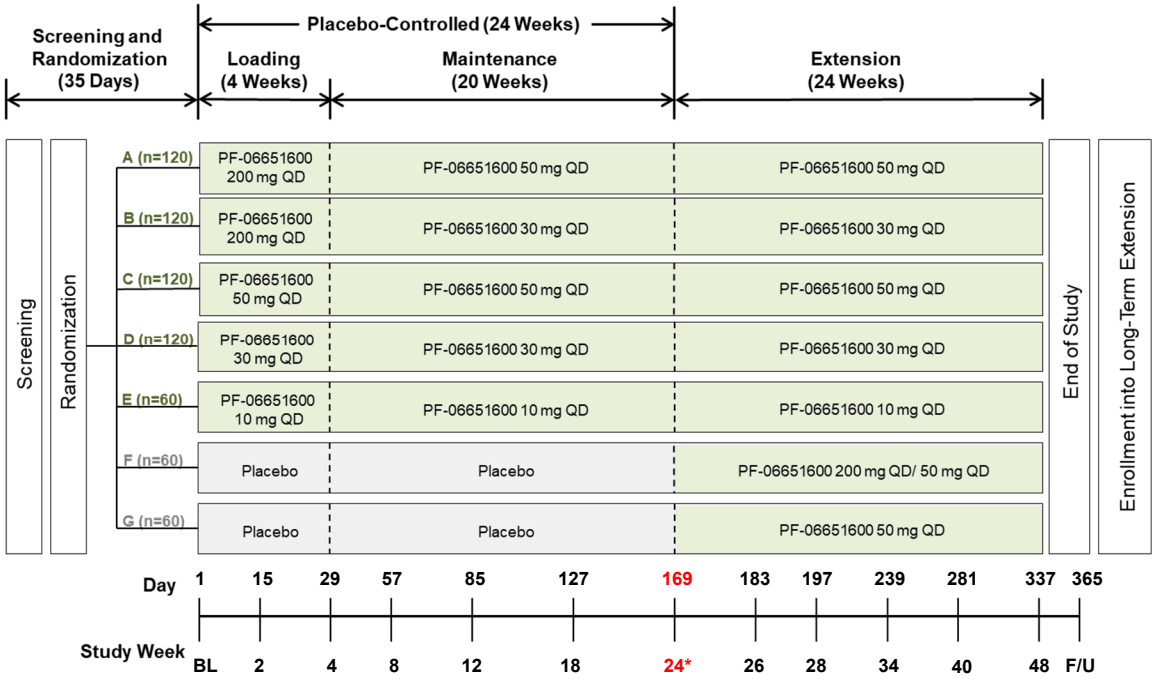
≥18 years of age and AT/AU; and

≥18 years of age and not AT/AU.

In these regions, subjects will be randomized using the same ratio as described for regions enrolling both adolescents and adults.

Figure 1 provides a schematic of the study design and the 7 treatment sequences. All subjects will begin dosing during the loading period according to their assigned sequence. Following the 4-week loading period, subjects will continue dosing according to their assigned sequence in the 20-week maintenance period. At the end of the maintenance period, placebo-treated subjects will be advanced in a prespecified, blinded manner to one of two active treatment sequences for the remainder of the study (through Week 48). Investigators, subjects, and the sponsor study team will be blinded as to treatment group throughout the duration of the study. Following the last dose of study drug, both discontinued and completed subjects will enter into a 4-week follow-up period for safety monitoring. Subjects who complete treatment may be eligible for enrollment in a long-term study (Phase 3 study B7981032). Subjects who enroll immediately into the B7981032 study will not be required to complete the 4-week follow-up period in this study.

Figure 1. Study Design Schematic



* Primary endpoint for the overall study is response based on absolute Severity of Alopecia Tool (SALT) Score ≤20 at

4. SUBJECT ELIGIBILITY CRITERIA

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

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

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

4.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject or a legally acceptable representative/parent(s)/legal guardian has been informed of all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male or female subjects age 12 years and older, inclusive, at time of informed consent/assent. Adolescent subjects below the age of 18 years will only be enrolled into this study if permitted by the sponsor, local competent authority, and institutional review board (IRB)/ethics committee (EC). Otherwise, only subjects 18 years or older (or age specified by applicable reviewer) will be enrolled in those countries, regions, or sites. Within VHP countries in the EMA, subjects must be aged 18 through 74 years at the time of informed consent.

4. Subjects must meet/comply with the following reproductive criteria:

   Females:

   Female subjects are eligible to participate if they are not pregnant or breastfeeding, and at least 1 of the following conditions applies:

   a. Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Section 4.3, 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.

      OR

   b. Is not a WOCBP (see definitions below):

      Women in the following categories are not considered WOCBP:

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

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

          Note: Documentation for any of the above categories 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.

- Postmenopausal female:

  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a high follicle stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or hormone replacement therapy (HRT). Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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. Documentation of this review should be included in the participant's medical record for the study.

Males:

Outside of VHP countries in the EMA, no contraceptive methods are required for male subjects in this study.

Within VHP countries in the EMA, male subjects are eligible to participate if they agree to the following requirements during the intervention period and for at least 90 days after the last dose of study intervention:

- Refrain from donating sperm.

AND

- Use one acceptable method of contraception as described in Section 4.3.

5. Must meet the following AA criteria:

   a. Have a clinical diagnosis of AA with no other etiology of hair loss (eg, telogen effluvium, androgenetic alopecia, etc.).

   b. ≥50% hair loss of the scalp, including alopecia totalis (AT) and alopecia universalis (AU), without evidence of terminal hair regrowth within 6 months at both the screening and baseline visits.

      - AT is defined as complete (100%) scalp hair loss.

      - AU is defined as complete (100%) scalp, facial, and body hair loss.

      - Percentage of hair loss on the scalp will be measured by SALT.

- Photographs taken at Screening must be submitted to the Sponsor or designee for verification of SALT score ≥50 and hair loss due to AA. Subjects must not be randomized until verification has been confirmed.

c. Current episode of hair loss ≤10 years.

6. If receiving permitted concomitant medications for any reason other than AA, subjects 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. Subject must be willing to stay on a stable regimen during the duration of the study (see Section 5.8).

7. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.

4.2. Exclusion Criteria

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

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

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

3. Other types of alopecia (including, but not limited to traction and scarring alopecia, telogen effluvium). Subjects with known androgenetic alopecia will be excluded.

4. Other scalp disease that may impact AA assessment (eg, scalp psoriasis, dermatitis, etc).

5. Active systemic diseases that may cause hair loss (eg, lupus erythematosus, thyroiditis, systemic sclerosis, lichen planus, etc).

6. 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).

   b. For subjects who had previous history of suicidal behaviors in the past >1 year to <5 years: “Yes” answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS or any lifetime history of serious or

recurrent suicidal behavior, a risk assessment must be performed, and documented, by a qualified mental health professional to assess whether it is safe for the subject to participate in the trial.

c. Clinically significant depression as indicated by the Patient Health Questionnaire - 8 Items (PHQ-8) total score ≥15.

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

NOTE: For any subject who has significant depression or any suicidal behavior, the subject will not be randomized and should be referred for appropriate evaluation and treatment.

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

8. Received any of the following treatment regimens specified in the timeframes outlined below:

   a. **At any time**: previous use of any JAK inhibitor for use in any disease indication or any non-B-cell selective lymphocyte-depleting agent (eg, alefacept, alemtuzumab).

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

   c. **Within 12 weeks** of first dose of study drug or 5 half-lives (if known), whichever is longer: other immunomodulatory biologic agents.

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

      - Other systemic treatments that could affect AA including:

        - Immunosuppressants (eg, cyclosporine A, azathioprine, methotrexate [MTX], sulfasalazine, mycophenolate mofetil [MMF], everolimus, ibrutinib).

        - Intralesional, oral, or injectable steroids.

        - 5α-Reductase inhibitors (5-ARIs) (eg, finasteride, dutasteride).

        - Oral minoxidil.

        - Spironolactone if used specifically for AA.

e. **Within 6 weeks** of first dose of study drug: vaccination with live or attenuated live vaccine.

f. **Within 4 weeks** of first dose of study drug: Ultraviolet B (UVB) phototherapy, Psoralen Ultraviolet A (PUVA) therapy, other phototherapy, contact immunotherapy (eg, diphenylcyclopropenone [DPCP], squaric acid dibutylester [SADBE], and 1-chloro-2,4-dinitrobenzene [DNCB]), topical irritants (eg, anthralin), and liquid nitrogen cryotherapy.

g. **Within 4 weeks** of first dose of study drug or 5 half-lives (whichever is longer): prohibited cytochrome P450 isoenzyme 3A (CYP3A) inducers as described in Appendix 4.

h. **Within 2 weeks** of first dose of study drug: topical treatments on areas under assessment (ie, scalp, eyebrows, eyelashes, and fingernails) that could affect AA (eg, steroid cream, medicated shampoo, minoxidil).

i. **Within 1 week** of first dose of study drug:

- Herbal medications with unknown properties or known effects for AA.
- Prohibited CYP3A substrates as described in Appendix 4 (within 7 days or 5 half-lives, whichever is longer).

j. Subjects with shaved heads must not enter the study until hair has grown back and is considered stable by the investigator.

9. Treatment anticipated with prohibited concomitant medication(s) (see Section 5.8.2 and Appendix 4) during the course of the study.

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

11. 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.

12. History of any lymphoproliferative disorder such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease.

13. History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

14. Adolescent subjects 12 to <18 years-old without one of the following:

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

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

15. 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).

16. Active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1 or superficial skin infection within 1 week prior to Day 1. NOTE: subjects may be rescreened after the infection resolves.

17. Significant trauma or major surgery within 1 month of the first dose of study drug.

18. Considered in imminent need for surgery or with elective surgery scheduled to occur during the study.

19. Known immunodeficiency disorder, including positive serology for human immunodeficiency virus (HIV) at screening, or a first-degree relative with a hereditary immunodeficiency.

20. Infection with hepatitis B or hepatitis C viruses according to protocol-specific testing algorithm.

    a. For hepatitis B, all subjects will undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Subjects who are HBsAg positive will not be eligible for this study. Subjects who are HBsAg negative but HBcAb positive will be reflex tested for hepatitis B surface antibody (HBsAb).

Additional reflex testing for hepatitis B virus DNA testing (HBVDNA) is also required for HBcAb positive subjects in countries in which Hep B prevalence has been reported at a rate of >5.0% or if required by local standard of care. Please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria. For Japan-specific requirements, see Appendix 5.1.

b. For hepatitis C, all subjects will undergo testing for hepatitis C antibody (HCVAb) during Screening.

- Subjects who are HCVAb positive will be reflex-tested for hepatitis C RNA (HCV RNA). Subjects 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 (QFT-G) test or positive or borderline T-SPOT®.*TB* (T-Spot) test performed within the 3 months prior to Baseline (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 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 subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a QFT-G test, a T-Spot test, nor a PPD test need be obtained. Details of the previous course of therapy (eg, medication(s) used, dose, duration of therapy) should be documented in the source documentation.

A chest radiograph should be obtained if not done within the 3 months prior to Screening. To be considered eligible for the study, the chest radiograph must be negative for active TB infection.

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

A subject who is being treated for latent TB infection can only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection,

documentation of an adequate treatment regimen, and prior approval of the Sponsor.

22. Abnormal findings on the Screening chest radiographs (eg, chest x-ray) including, but not limited to, presence of active TB, general infections, 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.

23. 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 interval corrected using Fridericia's correction factor QTc_F (QTc_F) prolongation (>450 milliseconds).

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

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

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

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

    c. Platelet count <150 × 109/L or <150,000/mm3;

    d. Absolute lymphocyte count of <0.8 x 109 /L (<800/mm3);

    e. Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 based on the age appropriate calculation;

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

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

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

25. Have an active history of alcohol or substance abuse within 1 year prior to Day 1.

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

4.3. Lifestyle Requirements

4.3.1. Contraception

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods, and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects 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 subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject (if WOCBP) or partner.

Males

Outside of VHP countries in the EMA, no contraception methods are required for male subjects in the study.

Within VHP countries in the EMA, male subjects must agree to one of the following contraception requirements during the intervention period and for at least 90 days after the last dose of investigational product.

1. Be abstinent from sexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

2. Use a male condom during sexual intercourse with a female of childbearing potential.

3. Have undergone a vasectomy (with the confirmed absence of sperm, considering that the spermatogenesis cycle is approximately 90 days).

Females

The following applies to female subjects who are considered WOCBP.

Highly Effective Contraceptive Methods

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

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion or bilateral tubal ligation.

5. Oral, intravaginal, transdermal, or injectable combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation used in combination with a barrier method.

   Acceptable barrier methods include:

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

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

6. Vasectomized partner.

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

7. Sexual abstinence.

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

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

4.3.2. Cosmetic Treatments/Applications

Following screening, subjects must not shave the hair on the scalp, eyebrows, or eyelashes for the duration of the study. Subjects wishing to keep their hair short are permitted to do so and an appropriate length should be discussed with the investigator to allow for assessment of hair re-growth.

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

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

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

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

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

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

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

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active

ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is PF-06651600.

Subjects will be randomized in a 2:2:2:2:1:1:1 manner to 1 of 7 treatment sequences using blinded PF-06651600 and matching placebo which are defined in Section 3.

5.1. Allocation to Treatment

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

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

5.2. Breaking the Blind

The study will be sponsor, subject, and investigator blinded.

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

5.3. Subject Compliance

Subject compliance will be verified by the accounting of investigational product at each visit. When investigational product is administered at the clinic, it will be administered by the appropriately designated staff at the investigator site.

Compliance of the investigational product will be monitored by delegated site personnel by the accounting of unused medication returned by the subject at the study visits. Compliance will be documented on the CRF and source document. If compliance is <80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects interrupting investigational product for more than 10 days between

visits must be discussed with the sponsor for possible withdrawal from the study. If the subject is over-compliant (>120%) with study drug (intentional or accidental) the investigator or designee is to counsel the subject and ensure correct understanding of the study drug dosing regimen. The investigator should contact the Pfizer Study Clinician promptly with any over-compliance that may potentially impact the safe use of study drug or that may result in a serious adverse event.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-06651600 and its matched placebo will be provided as tablets for oral administration. The designation "PF-06651600-15" may appear on labeling and indicates a salt. It is equivalent to "PF-06651600" with regard to this protocol. The 50 mg and 10 mg tablets and their matching placebos will be supplied in blister cards and labeled according to local regulatory requirements. Subjects will receive blinded labeled supplies throughout the study.

In order to achieve the proper dosage and maintain the blind throughout the study, tablets will be dispensed in a blinded fashion to ensure that all subjects, regardless of the assigned treatment sequence, will take the same number of tablets/day. To accomplish this, all subjects will take 7 tablets/day during the loading period, 4 tablets/day during the maintenance period, 7 tablets/day during the first 4 weeks of the extension period, and 4 tablets/day for the remainder of the extension period. The number and type of tablets taken per day for each treatment sequence is detailed in Table 2.

Table 2. Number and Type of Tablets for Each Treatment Sequence

Treatment Sequence	Loading Period Day 1 to Week 4 (No. of Tablets)	Maintenance Period Weeks 4 to 24 (No. of Tablets)	First 4 Weeks of Extension Period Weeks 24 to 28 (No. of Tablets)	Remainder of Extension Period Weeks 28 to 48 (No. of Tablets)
A	4 of 50 mg active 3 of 10 mg size pbo	1 of 50 mg active 3 of 10 mg size pbo	1 of 50 mg active 3 of 50 mg size pbo 3 of 10 mg size pbo	1 of 50 mg active 3 of 10 mg size pbo
B	4 of 50 mg active 3 of 10 mg size pbo	1 of 50 mg size pbo 3 of 10 mg active	4 of 50 mg size pbo 3 of 10 mg active	1 of 50 mg size pbo 3 of 10 mg active
C	1 of 50 mg active 3 of 50 mg size pbo 3 of 10 mg size pbo	1 of 50 mg active 3 of 10 mg size pbo	1 of 50 mg active 3 of 50 mg size pbo 3 of 10 mg size pbo	1 of 50 mg active 3 of 10 mg size pbo
D	4 of 50 mg size pbo 3 of 10 mg active	1 of 50 mg size pbo 3 of 10 mg active	4 of 50 mg size pbo 3 of 10 mg active	1 of 50 mg size pbo 3 of 10 mg active
E	4 of 50 mg size pbo 1 of 10 mg active 2 of 10 mg size pbo	1 of 50 mg size pbo 1 of 10 mg active 2 of 10 mg size pbo	4 of 50 mg size pbo 1 of 10 mg active 2 of 10 mg size pbo	1 of 50 mg size pbo 1 of 10 mg active 2 of 10 mg size pbo
F	4 of 50 mg size pbo 3 of 10 mg size pbo	1 of 50 mg size pbo 3 of 10 mg size pbo	4 of 50 mg active 3 of 10 mg size pbo	1 of 50 mg active 3 of 10 mg size pbo

Table 2. Number and Type of Tablets for Each Treatment Sequence

Treatment Sequence	Loading Period Day 1 to Week 4 (No. of Tablets)	Maintenance Period Weeks 4 to 24 (No. of Tablets)	First 4 Weeks of Extension Period Weeks 24 to 28 (No. of Tablets)	Remainder of Extension Period Weeks 28 to 48 (No. of Tablets)
G	4 of 50 mg size pbo 3 of 10 mg size pbo	1 of 50 mg size pbo 3 of 10 mg size pbo	1 of 50 mg active 3 of 50 mg size pbo 3 of 10 mg size pbo	1 of 50 mg active 3 of 10 mg size pbo

Abbreviations: No. = Number; Pbo = placebo.

5.4.2. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system at each visit. A qualified staff member will dispense the investigational product via unique container numbers on the blister cards provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the blister cards provided, and the tablets should not be removed from the blister until the investigational product is to be administered. Subjects/caregivers will be instructed to return the blister cards to the site at the next study visit.

5.5. Administration

Subjects will be provided clear dosing instructions.

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

Subjects should take their tablets from a single row in the blister card each day. Subjects should not take more than one row of tablets out of the blister card at a time as mixing tablets between rows may change the amount of active medication taken in that day. If a tablet is dropped or damaged, skip taking that tablet and note this on the diary card. Subjects should not take a tablet from another row.

Subjects should take the tablets orally according to the dosing instructions provided with the medication. **Subjects will be encouraged to take the medication in the morning whenever possible**. Subjects should take the medication at approximately the same time every day. However, **for study visit days**, subjects are to be instructed to refrain from dosing at home and are to take the dose in the clinic.

If a dose is missed and the interval to the next dose is <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.

PF-06651600 dose may be temporarily withheld for a maximum of 10 days between visits at the discretion of the investigator. Subjects interrupting investigational product for more than

10 days between visits must be discussed with the sponsor for possible withdrawal from the study.

5.6. Investigational Product Storage

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

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

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

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

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

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

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

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

5.7. Investigational Product Accountability

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

All study drug, including empty blister cards, must be returned to the investigator by the subject at every visit and at the end of the trial.

5.7.1. Destruction of Investigational Product Supplies

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

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

5.8. Concomitant Medications/Treatment(s)

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

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

5.8.1. Permitted Concomitant Medications

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

A subject who is receiving 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 CRF.

With the exception of those medications prohibited for use in Appendix 4, 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 Appendix 4.

Acetaminophen may be used intermittently (not to exceed 3 g/day). Subjects are not allowed any other investigational drugs or treatments during the study.

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

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

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

5.8.2. Prohibited Medications and Treatments

Subjects will abstain from all concomitant medications as described in Exclusion Criterion 8 and Section 4 of the protocol and Appendix 4. Medically necessary medications should not be discontinued without prior evaluation of acceptable alternatives, including consultation with prescribing health professional.

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

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 should be discontinued.

Subjects must also avoid prolonged exposure to the sun and avoid the use of tanning booths, sun lamps or other ultraviolet light sources during the study.

Prohibited Concomitant Medications/Treatments:

The following medications and treatments are prohibited for use during the study. Subjects who are treated with any prohibited medication or treatment during the course of the study may be discontinued. NOTE: Examples provided do not represent an all-inclusive list of

medications and treatments. If there is a question about whether a particular medication is prohibited, the medication should be discussed with the sponsor.

- Medications and treatments that could affect AA:
  - JAK inhibitors for use in any disease indication.
  - Immunosuppressants (eg, cyclosporine A, azathioprine, methotrexate [MTX], sulfasalazine, mycophenolate mofetil [MMF], everolimus, ibrutinib).
  - Intralesional, oral or injectable steroids.
  - 5α-Reductase inhibitors (5-ARIs) (eg, finasteride, dutasteride).
  - Oral minoxidil.
  - Spironolactone if used specifically for AA.
  - Other systemic treatments that could affect AA.
  - Topical treatments that could affect AA on areas under assessment (ie, scalp, eyebrows, eyelashes, and fingernails) (eg, steroid cream, medicated shampoo, minoxidil).
  - Phototherapy (eg, Ultraviolet B [UVB] phototherapy, Psoralen Ultraviolet A [PUVA]).
  - Contact immunotherapy (eg, diphenylcyclopropenone [DPCP], squaric acid dibutylester [SADBE], and 1-chloro-2,4-dinitrobenzene [DNCB]).
  - Topical irritants (eg, anthralin) and liquid nitrogen cryotherapy.
  - Cosmetic treatments/applications as described in Section 4.3.2.
- Medications with potential drug-drug interactions or potential safety concerns:
  - Lymphocyte-depleting agents/therapies, including both non-B-cell selective and B-cell-depleting agents (eg, alefacept, alemtuzumab, rituximab).
  - Other biologics with immunomodulatory properties.
  - Live (attenuated) vaccines: restrictions on vaccinations are described in more detail in Section 5.8.3.
  - Moderate to potent CYP3A inducers (See Appendix 4).
  - Specific sensitive to moderate sensitive CYP3A substrates (See Appendix 4).

- Herbal medications with either unknown properties or pharmaceutical properties that impact AA.
- Investigational compounds.

5.8.3. Vaccinations

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 6 weeks prior to the first dose of study drug, during the study, and for 6 weeks after the last dose of investigational product. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during study treatment and for 6 weeks following completion of study treatment. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

Such vaccines include but are not limited to: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine, vaccinia (smallpox) vaccine, and Zostavax® (zoster vaccine live).

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

5.8.4. 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. Subjects who have elective surgery should temporarily discontinue study intervention for 1 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.

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

6. STUDY PROCEDURES

Refer to the Schedule of Activities for a detailed list of study procedures as they should be conducted at each respective visit. Visit windows are based on Day 1 visit.

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

To assure consistency and reduce variability, visits should occur at approximately the same time of day throughout the study. Subjects should be encouraged to attend visits in the morning and prior to the subject's dosing of investigational product as subjects 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 investigational product for female subjects of childbearing potential through end of study (EOS). In addition to urine pregnancy tests performed at each study visit, sites in VHP countries in the EMA should instruct female subjects of childbearing potential to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44). In addition, the investigator or designee will instruct the subject to contact the site immediately if the urine pregnancy test result is positive or cannot be confirmed as negative. The list of VHP countries participating in the protocol can be found in Section 4.

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

Refer to Appendix 3 for guidelines on subject safety monitoring and discontinuation.

6.1. Screening, Visit 1

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

Due to possible need for tuberculin testing and chest radiograph, as well as to allow time for verification of SALT scores, screening procedures may be performed over more than 1 visit within the 35 days prior to the Day 1 visit.

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

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

The following procedures will be completed:

- Obtain written informed consent (or parent(s)/legal guardian and assent from the subject, as appropriate).

- Register subject in Impala.
- Review Inclusion and Exclusion criteria.
- Administer patient reported outcome (PRO) questionnaire: Patient Health Questionnaire – 8 items (PHQ-8).
- Collect demography.
- Complete AA disease history includes collection of details of AA at Screening: AA background, AA history, AA diagnosis, pattern of scalp hair loss, body hair loss, nail involvement, the use of topical treatments, systemic treatments and other treatments for AA used at any time prior to the Screening visit.
- Complete medical history, in addition to AA history, including but not limited to comorbidities associated with AA, history of drug, alcohol, tobacco use, skin rash, and infection will be collected at Screening. Smoking status and alcohol consumption will also be collected.
- Obtain complete medication history of all other prescription or nonprescription drugs, and dietary and herbal supplements taken within 35 days prior to the Screening Visit.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Perform single 12-lead ECG.
- Obtain height and weight.
- Conduct complete physical examination including dermatological full body examination.
- Perform audiological evaluation (unless performed within 8 weeks of Day 1).
- Perform chest radiograph (if previous chest radiograph has not been performed within 3 months prior to Screening visit; this may be performed at a different location outside of the study site).
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, serum FSH (in female subjects under 60 years-old and who have been amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause to confirm postmenopausal status), urine pregnancy test (female subjects of childbearing potential), and testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B reflex testing (if applicable) (See Appendix 5.1 for Japan-specific requirements), hepatitis C antibody (HCVAb), and hepatitis C reflex testing (if applicable).

- In all adolescent subjects, confirm presence or absence of documented evidence of having received varicella vaccination (2 doses).

- Only in adolescent subjects who have no documented evidence of having received varicella vaccination (2 doses): perform VZV IgG Ab testing to confirm eligibility.

- Perform TB testing (unless performed within 12 weeks of Day 1). QFT-G test is preferred; however, the T-Spot is also permitted. If Mantoux PPD tuberculin skin test is performed, the subject must return between 48-72 hours post-injection for evaluation of induration (see Section 7.5.8 for further details on TB testing).

- Take scalp photographs to verify eligibility. Take eyelash and eyebrow photographs.

- Conduct clinical evaluations: Severity of Alopecia Tool (SALT), Eyebrow Assessment (EBA), Eyelash Assessment (ELA), and CGI-AA.

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

- Assess need for contraception and adherence to applicable lifestyle requirements (see Section 4.3). Establish willingness and ability to comply with lifestyle requirements going forward in study.

- Assess for occurrence of SAEs and non-serious AEs: the reporting period starts with the signing of the informed consent.

6.2. Study Period

The visit window for all visits during the study period is based on the date of Visit 2, Day 1 (Randomization).

6.2.1. Visit 2, Day 1 (Randomization)

Prior to randomizing the subject in Impala, the inclusion/exclusion criteria must be reviewed against all information/results from Visit 1 (screening) in addition to information collected at Visit 2 (randomization) including prior/concomitant medications, changes in medical conditions, physical exam findings, pregnancy test results, contraception check, C-SSRS results, and SALT score. NOTE: Subject eligibility, as based on external review of Screening photographs, must be available prior to randomization. At any time during the Day 1 visit, if it is determined that the subject does not meet eligibility criteria, it is not necessary to perform any further assessments at Day 1.

The following procedures will be completed:

- Administer PRO questionnaires: Alopecia Areata Patient Priority Outcomes (AAPPO), Hospital Anxiety and Depression Scale (HADS), 36-Item Short Form Health Survey version 2 Acute (SF36v2 Acute), Alopecia Areata Resource Utilization (AARU), Work Productivity and Activity Impairment: Alopecia Areata

(WPAI:AA) in adults, and EuroQoL 5 Dimensions (EQ-5D-5L) in adults or EuroQol 5 Dimension – Youth (EQ-5D-Y) in adolescents.

- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Capture photographs.
- Conduct clinical evaluations: SALT, EBA, ELA, assessment of fingernails affected by AA, and CGI-AA. NOTE: subjects who experience any terminal hair regrowth between the Screening and Day 1 visits are not eligible for randomization.
- Conduct C-SSRS.
- Review any changes in the subject's prior and concomitant treatment information.
- Review medical history and AA disease history.
- Assess for occurrence of AEs: The reporting period starts with the signing of the informed consent.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Obtain height and weight.
- Conduct complete physical examination.
- Perform single 12-lead ECG.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for other laboratory testing: hematology, serum chemistry, urinalysis, interferon gamma-induced protein 10 (IP-10), fluorescence-activated cell sorting for T-cells, B-cells, and natural killer (NK) cells (FACS-TBNK), and immunoglobulins (IgA, IgG, IgM).
- Collect sample for viral screen.

- Collect a genomic banked biospecimen (Prep D1). If missed, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.
- Obtain Prep B1, B2, and R1 samples.
- Review of Inclusion/Exclusion Criteria.
- If subject meets all Inclusion/Exclusion criteria, randomize subject into the study in Impala.
- **Prior to dosing**, obtain samples for PK analysis.
- Administer first dose of study drug to subject.
- Provide and review dosing instruction.
- Dispense study drug supply to the subject.

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

The following procedures will be completed:

- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Obtain samples for other laboratory testing: hematology.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.3. Visit 4, Day 29/Week 4 (±3 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, P-Sat, HADS, SF36v2 Acute, and EQ-5D-5L in adults or EQ-5D-Y in adolescents.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Perform single 12-lead ECG.
- Conduct targeted physical examination.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, IP-10, and FACS-TBNK.
- Obtain Prep B1, B2, and R1 samples.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Capture photographs.
- Conduct clinical evaluations: SALT, EBA, ELA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- **Prior to dosing**, obtain sample for PK analysis and then at 0.5 hour, 1 hour, and 3 hours after dosing.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.4. Visit 5, Day 57/Week 8 (±7 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, P-Sat, HADS, and SF36v2 Acute.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Conduct targeted physical examination.
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, and IP-10.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Conduct clinical evaluations: SALT, EBA, ELA, and CGI-AA.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Prior to dosing, obtain sample for PK analysis and then at 0.5 hour and 2 hours after dosing.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.5. Visit 6, Day 85/Week 12 (±7 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, P-Sat, HADS, SF36v2 Acute, AARU, WPAI: AA in adults, and EQ-5D-5L in adults or EQ-5D-Y in adolescents.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.

- Conduct targeted physical examination.
- Obtain fasting samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, HBVDNA (if applicable), IP-10, and FACS-TBNK.
- Obtain Prep B1, B2, and R1 samples.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Capture photographs.
- Conduct clinical evaluations: SALT, EBA, ELA, assessment of fingernails affected by AA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Prior to dosing, obtain sample for PK analysis and then at 0.5 hour and 2 hours after dosing. If PK samples were collected at Week 8, no PK samples are required at Week 12.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.6. Visit 7, Day 127/Week 18 (±7 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, and P-Sat.

- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Conduct targeted physical examination.
- Obtain samples for laboratory testing: hematology, blood chemistry, and urinalysis.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Conduct clinical evaluations: SALT, EBA, ELA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.7. Visit 8, Day 169/Week 24 (±7 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, P-Sat, HADS, SF36v2 Acute, AARU, WPAI: AA in adults, and EQ-5D-5L in adults or EQ-5D-Y in adolescents.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Perform single 12-lead ECG.
- Obtain height and weight.
- Conduct complete physical examination.

- Perform audiological evaluation.
- Obtain fasting samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, HBVDNA (if applicable), IP-10, FACS-TBNK, and immunoglobulins (IgA, IgG, IgM).
- Obtain Prep B1, B2, and R1 samples.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Capture photographs.
- Conduct clinical evaluations: SALT, EBA, ELA, assessment of fingernails affected by AA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.8. Visit 9, Day 183/Week 26 (±3 days)

The following procedures will be completed:

- Perform urine pregnancy test (female subjects of childbearing potential only).
- Obtain samples for other laboratory testing: hematology.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish

willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.9. Visit 10, Day 197/Week 28 (±3 days)

The following procedures will be completed:

- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Conduct targeted physical examination.
- Perform single 12-lead ECG.
- Obtain fasting samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, and urinalysis.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Conduct clinical evaluations: SALT, EBA, ELA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Capture photographs.

- Assess for occurrence of AEs.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.10. Visit 11, Day 239/Week 34 (±7 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, P-Sat, AARU, and WPAI: AA in adults.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Conduct targeted physical examination.
- Obtain fasting samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, and HBVDNA (if applicable).
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Conduct clinical evaluations: SALT, EBA, ELA, assessment of fingernails affected by AA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.

- Provide and review dosing instruction.
- Dispense new study drug to the subject.

6.2.11. Visit 12, Day 281/Week 40 (±7 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, and P-Sat.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Conduct targeted physical examination.
- Obtain samples for laboratory testing: hematology, blood chemistry, and urinalysis.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) going forward in study.
- Perform urine pregnancy test (female subjects of childbearing potential only). In addition to urine pregnancy tests performed at each study visit, sites in VHP countries in VHP countries in the EMA should instruct female subjects of childbearing potential to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44). In addition, the investigator or designee will instruct the subject to contact the site immediately if the urine pregnancy test result is positive or cannot be confirmed as negative. The list of VHP countries participating in the protocol can be found in Section 4.
- Confirm proper contraception is being used.
- Conduct clinical evaluations: SALT, EBA, ELA, assessment of fingernails affected by AA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Collect study drug from subject, administer dose to subject, and perform accountability procedures.
- Provide and review dosing instruction.

- Capture photographs.
- Dispense new study drug to the subject.

6.2.12. Visit 13, Day 337/Week 48/End of Treatment (±7 days)

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, P-Sat, HADS, SF36v2 Acute, AARU, WPAI: AA in adults, and EQ-5D-5L in adults or EQ-5D-Y in adolescents.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Perform single 12-lead ECG.
- Obtain height and weight.
- Conduct complete physical examination.
- Perform audiological evaluation.
- Obtain fasting samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, HBVDNA (if applicable), FACS-TBNK, and immunoglobulins (IgA, IgG, IgM).
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) through 28 days after the last dose of study medication.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Capture photographs.
- Conduct clinical evaluations: SALT, EBA, ELA, assessment of fingernails affected by AA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.

- Collect study drug from subject and perform accountability procedures.

6.3. Follow-up Period

6.3.1. Visit 14, End of Study/Follow-up

If a subject discontinues from the study for any reason other than death, lost to follow-up, or withdrawal of consent, a Follow-Up Visit must be performed within 28 (+7 days) after the Early Termination visit. In addition, all subjects who complete the study but do not enter the long-term extension study must have a Follow-Up Visit within 28 (+7 days) of End of Treatment visit.

The following procedures will be completed:

- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.
- Conduct targeted physical examination.
- Obtain fasting samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, and urinalysis.
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.

6.3.2. Early Termination Visit

For subjects who discontinue early from the study, the procedures scheduled for early termination (ET) Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. Subject will then require a Follow-up visit occurring within 28 (+7 days).

The following procedures will be completed:

- Administer PRO questionnaires: AAPPO, PGI-C, P-Sat, HADS, SF36v2 Acute, AARU, WPAI: AA in adults, and EQ-5D-5L in adults or EQ-5D-Y in adolescents.
- Obtain vital signs: pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest), and temperature.

- Perform single 12-lead ECG.
- Obtain height and weight.
- Conduct complete physical examination.
- Perform audiological evaluation.
- Obtain fasting samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, urinalysis, HBVDNA (if applicable), FACS-TBNK, and immunoglobulins (IgA, IgG, IgM).
- Confirm whether menarche has started in previously premenarchal subjects. If menarche has started, the subject must undergo a pregnancy test and establish willingness and ability to comply with contraception requirements (see Section 4.3) through 28 days after the last dose of study medication.
- Perform urine pregnancy test (female subjects of childbearing potential only).
- Confirm proper contraception is being used.
- Capture photographs.
- Conduct clinical evaluations: SALT, EBA, ELA, assessment of fingernails affected by AA, and CGI-AA.
- Conduct C-SSRS.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of AEs.
- Collect study drug from subject and perform accountability procedures.

6.4. Subject Withdrawal/Early Termination

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

Subjects who discontinue study treatment from the Treatment Period for any reason other than death, lost to follow-up, or withdrawal consent will enter into the Follow-up Period (see Withdrawal of Consent section below). The procedures scheduled for Early Termination Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. Subjects will then require a Follow-Up Visit within 28 (+7 days). In

addition, all subjects who complete the study but do not enter the open-label extension study must have a Follow-Up Visit within 28 (+7 days) of End of Treatment visit.

See Appendix 3 for guidelines on subject safety monitoring and discontinuation. The Early Termination Visit only applies to subjects who are randomized, received at least one dose of study drug, and then are prematurely withdrawn from the study treatment.

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

Withdrawal of consent:

Every effort will be made to complete Early Termination and Follow-up Visits as described above for subjects who request to discontinue receipt of study treatment during the Treatment Period (withdrawal consent). The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

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

Lost to follow-up:

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

complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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

7. ASSESSMENTS

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

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

If subject visits or procedures are affected by a public emergency, including the COVID-19 pandemic, please refer to Appendix 6.

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

In female subjects who are premenarchal at the start of the study, the investigator must confirm with the subject at every visit whether menarche has started since the last visit. If menarche has started, the subject must now be considered of childbearing potential; therefore, from that point forward and starting with the current visit, the subject will be required to establish willingness and ability to comply with contraception requirements (see Section 4.3) and to undergo contraception checks and pregnancy testing according to the Schedule of Activities, starting with the current visit. In addition, the investigator or designee will instruct the subject to contact the site immediately if the subject begins menarche between study visits.

7.2. Pregnancy Testing

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

Pregnancy tests must have a sensitivity of at least 25 mIU/mL. Pregnancy tests should be urine pregnancy tests. In the event that urine pregnancy tests are not permitted at an institution, serum pregnancy tests can be utilized. Pregnancy tests will be performed in WOCBP at the times listed in the Schedule of Activities. Following a negative pregnancy

test result at screening, appropriate contraception must be verified, and a second negative pregnancy test result will be required at the baseline visit prior the subject receiving the investigational product. 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 subject must be excluded if the serum pregnancy result is positive. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product but may remain in the study for follow-up.

In addition to urine pregnancy tests performed at each study visit, sites in VHP countries in the EMA should instruct female subjects of childbearing potential to perform a urine pregnancy test at home between the Week 40 and 48 visits (at approximately Week 44). In addition, the investigator or designee will instruct the subject to contact the site immediately if the urine pregnancy test result is positive or cannot be confirmed as negative. The list of VHP countries participating in the protocol can be found in Section 4.

7.3. Banked Biospecimens

Banked biospecimens will be collected from subjects for exploratory research relating to the drug response and disease/condition under study. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the Schedule of Activities section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism

of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

Additional banked biospecimens to be retained for such exploratory analyses in this study include the following:

- **Prep B1 (K2EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis):** a 10-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- **Prep B2 (serum collection optimized for biomarker/proteomic/metabonomic analysis):** a 10-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- **Prep R1 (PAXGene whole-blood collection optimized for RNA analysis):** A 2.5 mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

The banked biospecimens will be collected from all subjects unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document that they will not be compensated in this event.

7.4. Additional Research

Unless prohibited by local regulations or IRB/EC decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Subjects may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.5. Safety Assessments

Safety will be assessed by the spontaneous reporting of AEs, physical examinations and clinical laboratory results in all subjects who receive at least one dose of the investigational product. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Investigators and Pfizer Clinicians (or designees) will review individual subject data throughout the conduct of the study to ensure subjects' well-being.

7.5.1. Vital Signs

Vital signs (pulse rate, blood pressure, respiratory rate and oral, tympanic, or axillary temperature) will be measured after 5 minutes of rest as indicated in the Schedule of Activities.

Vital signs should be performed before laboratory blood collection and ECG.

It is preferred that body temperature be collected using the tympanic or oral methods; however, the axillary and temporal artery methods are also permitted. The same method will be used consistently throughout the study.

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

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

Pulse rate should be measured at approximately the same time as BP for a minimum of 30 seconds.

7.5.2. Medical History, Physical Exam, Height, and Weight

Complete AA disease history includes collection of details of AA at Screening: AA history, AA diagnosis, pattern of scalp hair loss, body hair loss, nail involvement, the use of topical treatments, systemic treatments and other treatments for AA. Medical history, in addition to AA history, including, but not limited to, comorbid conditions, history of drug, alcohol, tobacco use, dermatologic history, and infection will be collected at Screening and baseline (if applicable). Smoking status and average weekly alcohol consumption (units/week) will also be collected.

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

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

dermatological full body exam must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Dermatological examinations should also include visual inspection of the breasts and external genitalia.

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

When dermatologic adverse events are identified on physical exam, additional procedures may be required. Please refer to Section 7.5.6.2 for additional details.

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

Complete and Targeted physical examinations are performed at various time points, see Schedules of Activities.

7.5.3. Chest Radiography

Chest X-ray (posterior-anterior and lateral views are recommended, however local guidelines should be followed) or other appropriate diagnostic image (ie, computed tomography or magnetic resonance imaging [MRI]) should be taken at Screening or within 3 months prior to Screening visit and read by a qualified radiologist or pulmonologist and must show no evidence of abnormalities including but not limited to current, active TB or previous inactive TB, general infections, heart failure or malignancy. Documentation of the official reading must be located and available in the source documentation.

7.5.4. Electrocardiogram (ECG)

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

ECG should be performed before laboratory blood collection.

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

The Screening ECG values will serve as each subject's baseline values. To ensure safety of the subjects, qualified medical personnel will review all ECGs and make comparisons to Screening measurements. A paper or digital copy of the ECG should be filed in the subject's chart and must be available to the sponsor upon request. Any clinically significant changes will be recorded and evaluated further, as clinically warranted. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. Subjects will be discontinued from study with a confirmed QTc_F >500 milliseconds or a confirmed QTc_F change from baseline of >60 milliseconds.

7.5.5. Audiological Evaluation

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

A full audiological evaluation must be completed at Screening or within 8 weeks prior to Day 1. This evaluation includes audiological history, otoscopic examination, pure tone audiometry, air and bone conduction, speech audiometry, and immittance audiometry. All audiological results must be available prior to Day 1 to assess eligibility.

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

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

If there is a clinically meaningful, treatment-emergent decline in hearing from baseline, the subject must be promptly evaluated by a medically qualified specialist to assess for possible causes. Evaluation results should then be discussed with the Sponsor to determine if the subject should be discontinued from the study. Discontinued subjects must be followed up off-treatment with appropriate testing at regular intervals, until hearing returns to baseline or is determined to be clinically stable.

Refer to the most current version of the Audiometry Study Guide for details on auditory evaluation. All procedures must be performed as per the Audiometry Study Guide.

7.5.6. Special Safety Assessment

7.5.6.1. 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.

7.5.6.2. Dermatological Events

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

Guidelines for the assessment of herpetiform rash and drug-related rash are noted in Sections 7.5.6.2.1 and 7.5.6.2.2, respectively.

7.5.6.2.1. Herpetiform Rash

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and 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.

7.5.6.2.2. Potential Drug-Related Rash and Unexplained Rash

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

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

All subjects reporting an unexplained skin rash should undergo a formal comprehensive dermatologic evaluation. In addition, the subject 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 subject refuses to have biopsy performed. The biopsy will be sent to the local laboratory for histological investigation of the rash in order to gain insight into potential etiology of the rash.

In addition to a biopsy of suspected drug-related rash, a swab (for microbiological assessment) of the affected area will also be taken for culture and sensitivity to assess (at the local laboratory) for any bacterial, fungal, or viral pathogens, if applicable.

Photographs of the rash will be taken.

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

7.5.7. Clinical Laboratory Tests

The following laboratory tests (Table 3) will be performed at time points identified in the Schedule of Activities. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns at the investigator's discretion.

Sample collection, labeling, storage, and shipping information can be found in the laboratory manual. All laboratory tests with clinically important changes from baseline identified after administration of investigational product will be followed until the value stabilizes. In addition, there are laboratory results which require specific follow-up described in Appendix 3.1 Monitoring Criteria.

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

Table 3. Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (performed by the central laboratory)	Other
Hemoglobin	BUN or Urea	pH	FSH[a]
Hematocrit	Creatinine	Glucose	Pregnancy tests[b]
Red blood cell count	Glucose	Protein	HIV[c]
Platelet count	Calcium	Blood	HBsAg
White blood cell count	Sodium	Ketones	HBcAb
Total neutrophils (%, Abs)	Potassium	Nitrites	HBsAb[d]
Basophils (%, Abs)	Chloride	Leukocyte esterase	HBVDNA[e]
Eosinophils (%, Abs)	Total CO_2 or Bicarbonate	Urobilinogen	HCVAb
Lymphocytes (%, Abs)[f]	AST	Urine bilirubin	HCVRNA[g]
Monocytes (%, Abs)	ALT	Microscopy[h]	VZV IgG Ab[i]
Reticulocyte count (%, Abs)	Total bilirubin	Urine culture[j]	QFT-G test or T-Spot test[k]
	Direct and indirect bilirubin		Viral screen[l]
	Alkaline phosphatase		Ig subtypes
	Uric acid		Skin biopsies/swabs[m]
	Albumin		IP-10[n]
	Total protein		Fasting lipid profile[o]
	Creatine kinase[p]		T cell, B cell and NK cell subsets
	Follow-up testing for potential DILI cases[q]		

a. In females under 60 years old and who are amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause to confirm postmenopausal status.
b. Pregnancy tests (urine) for women of childbearing potential. In the event that urine pregnancy tests are not permitted at an institution, serum pregnancy tests can be utilized.
c. HIV testing per local regulations. Subjects who are positive for HIV antibodies will be screen-failed.
d. HBsAb will be performed as reflex testing for any subject who is HBsAg negative but HBcAb positive. For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at screening for all subjects rather than as a reflex test. For Japan-specific requirements see Appendix 5.1. For all other countries, please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria.
e. HBVDNA testing will be performed at Week 12 for subjects who were enrolled with a positive HBcAb and a negative HBVDNA in those regions for which Hep B prevalence has been reported at a rate of >5.0% or if required by local standard of care (refer to Section 7.5.11 for information regarding which screening laboratory results should be used to determine whether HBVDNA testing should be performed). Testing at additional time points may be performed as per the local standard of care. For Japan specific requirements see Appendix 5.1. For all other countries, please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria.
f. Subjects 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.
g. HCVRNA will be performed as reflex testing for any subject who is HCVAb positive.
h. Only if urine dipstick is positive for blood, nitrites, leukocyte esterase, and/or protein.
i. VZV IgG Ab testing is required to confirm eligibility only in adolescent subjects who do not have documented evidence of having received varicella vaccination (2 doses).
j. Urine culture will be performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.
k. The QFT-G test is preferred; however, the T-Spot test is also permitted. A negative PPD test can be substituted for the QFT-G test or T-Spot test only under specific circumstances described in Section 7.5.8.
l. A serum sample will be collected at baseline 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 subject had exposure to that virus.
m. When required in cases of skin rash adverse events. See applicable sections for herpetiform rash (Section 7.5.6.2.1) and potential drug-related rash (Section 7.5.6.2.2).
n. After randomization, the investigator and Pfizer study personnel directly involved in the conduct of the trial will be kept blinded of the results of this test.
o. 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.
p. Urine myoglobin will be performed as reflex testing for any subject with a creatine kinase >10 × ULN.
q. In cases of suspected potential drug-induced-liver-injury (DILI), follow-up testing should be performed according to requirements in Section 8.4.2.

Clinically significant abnormal findings should be recorded as AEs. Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Clinically significant laboratory findings at the final assessment should be followed up to resolution or until determined by the Investigator to be stabilized. Repeat tests may be indicated to establish this. Refer to Appendix 3 for laboratory discontinuation criteria.

7.5.8. Tuberculosis Testing

During the Screening period, it must be determined and documented that a subject does not have evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB) per the Inclusion Criteria. The results of TB screening conducted in the 12 weeks prior to Day 1 visit or during the Screening period must be documented in study records prior to Baseline (Visit 2).

QuantiFERON®-TB Gold In-Tube (QFT-G) test is the preferred testing method; however, the T-SPOT®.*TB* (T-Spot) test is also permitted. Borderline results from the T-Spot test should be considered an exclusionary test result for this study.

If the laboratory reports that the QFT-G test or T-Spot test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, then subjects may be screened using the Purified Protein Derivative (PPD) Tuberculin Skin Test (Mantoux method) with approval of the Pfizer Medical Monitor.

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 at screening for either the QFT-G or the T-Spot testing. The site must determine which test will be performed as sample collection and processing guidelines differ. QFT-G testing will be performed at the central laboratory and T-Spot testing will be performed at the site's local laboratory. Following QFT-G sample processing, the sample will be shipped to the central laboratory for testing. The procedure for processing and preparing the sample for shipment is described fully in the laboratory manual, which will be provided to investigators.

In addition to TB testing as specified in this clinical protocol, a chest X-ray will be performed as described in Section 7.5.3.

7.5.8.1. 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 subjects may be screened using the PPD Tuberculin Test (Mantoux method), with the approval of the Pfizer Medical Monitor.

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

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

Only adolescent subjects without documented evidence of having received varicella vaccination (2 doses) will be tested for VZV IgG Ab as described in the lab manual.

7.5.10. Baseline Viral Screen

A serum sample will be collected at baseline 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 subject had exposure to that virus. Additional sample collection instructions will be provided in the lab manual. The retained samples will be destroyed upon subject completion of this study or the long-term extension study.

7.5.11. Hepatitis B DNA (HBVDNA) Testing

For subjects in countries in which hepatitis B prevalence has been reported at a rate of >5.0%[59] or if required by local standard of care, HBVDNA testing will be performed as reflex testing for any subject who is HbcAb positive at screening. In addition, HBVDNA testing will be performed at Weeks 12, 24, 34, 48, and Early Termination for subjects who were enrolled with a positive HBcAb and a negative HBVDNA in those regions for which hepatitis B prevalence has been reported as a rate of >5.0% or if required by local standard of care. Testing at additional time points may be performed as per the local standard of care. Please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria; for Japan-specific requirements, see Appendix 5.1.

7.5.12. Events for Adjudication/Review Committee Submission

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, or malignancy events may also be identified by the Pfizer Study Team or designee during the review of subject data listings or by site monitors during routine monitoring of subject's study records. Additional types of events for review and adjudication may be identified by Pfizer. The Pfizer Study Team or designee will notify the study site of any 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 and death certificate information, as applicable.

7.6. Clinical Assessments

7.6.1. Severity of Alopecia Tool (SALT)

Severity of alopecia tool (SALT) is a quantitative assessment of AA severity based on scalp terminal hair loss.

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.

Subject must have a SALT score ≥50 at both Screening and Baseline to be eligible for the study.

Photographs of scalp taken at the Screening visit will be reviewed by an independent consultant to confirm the SALT scores; photographs taken at other study visits may also be reviewed. For more information on photography required for this protocol, see Section 7.9.

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

7.6.2. Eyelash Assessment (ELA)

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

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

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

Mascara and false eyelashes must be removed for clinical assessments of AA at all study visits.

7.6.3. Eyebrow Assessment (EBA)

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

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

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

7.6.4. Assessment of Fingernails Affected by Alopecia Areata

The number of fingernails affected by AA will be counted in all subjects at baseline. The number of affected fingernails will be counted at subsequent visits during the study treatment period (see Schedule of Activities). Fingernails may have any of the following changes to be considered "affected": nail pitting; trachyonychia (roughening of nail surface); onychorrhexis (brittle nails); koilonychia (transverse and longitudinal concavity of nail, ie, "spoon shaped"); onychomadesis (separation of nail plate from nail bed); longitudinal ridging or striations; leuconychia (white lines or spots in nail plate); red spotting of the lunulae.[58,60-76]

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

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

7.6.5. Clinician Global Impression – Alopecia Areata (CGI-AA)

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

7.7. Assessment of Suicidal Ideation and Behavior

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

Columbia suicide severity rating scale is a validated tool to evaluate suicidal ideation and behavior.

There are 2 versions of the C-SSRS to be utilized in this study - "C-SSRS for screening and baseline visits" and "C-SSRS for any post-baseline visits". The version used is dictated by the actual study visit.

At Screening or Day 1 visits, if the subject has had suicidal ideation associated with actual intent and a method or plan in the past year ("yes" answers on items 4, 5), the subject will not be included in the study. For subjects who have had previous history of suicidal behaviors in the past 5 years, a risk assessment must be performed and documented by a qualified mental health professional to assess whether it is safe for the subject to participate in the trial.

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

At any post-baseline visits, if there are "yes" answers on items 4, 5, or on any question in the suicidal behavior section of the C-SSRS, the subject will be discontinued from the study and referred to a mental health professional for appropriate evaluation and treatment. If the subject cannot be seen by a mental health professional within 24 hours, then the subject should be sent to a local emergency room for psychiatric assessment.

7.8. Patient Reported Outcome (PRO)

Every effort should be made to have the subject complete all patient reported outcome questionnaires before any other evaluations. All PROs should be completed as per Schedule of Activities.

7.8.1. Alopecia Areata Patient Priority Outcomes (AAPPO)

The Alopecia Areata Patient Priority Outcomes (AAPPO) scale is a self-administered questionnaire that measures hair loss, emotional symptoms, and activity limitations over the past week. This measure was developed based on qualitative patient input as well as review of other data sources (eg, literature, expert input, other existing measures, etc.). The first four items of the tool, which cover hair loss from the scalp, eyebrows, eyelashes, and body, ask the patient to describe the current amount of hair loss using a 5 point response scale that ranges from "no hair loss" to "complete (do not have any hair on my [insert body area])." The remaining items ask the patient to rate the impact of AA over the past week on a 5-point scale ranging from "never" to "always." The PGI-C and P-Sat enable an anchor-based method for interpreting meaningful changes in the AAPPO domain scores.

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

The Patient's Global Impression of Change (PGI-C) asks the subject 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 patients will select one of seven responses ranging from "greatly improved" to "greatly worsened."

7.8.3. Patient Satisfaction with Hair Growth (P-Sat)

The Patient Satisfaction with Hair Growth (P-Sat) asks the subject to evaluate his/her satisfaction with the hair that has regrown since the start of the study. This measure is comprised of three items asking about satisfaction with the "amount" and "quality" of hair as well as "overall" satisfaction with the hair. The patients will select one of seven responses ranging from "very satisfied" to "very dissatisfied."

7.8.4. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week. Items are rated on a 4-point severity scale. The HADS produces 2 scales, one for anxiety (HADS–A) and one for depression (HADS–D), differentiating the two states with established normal score cut-offs.[79,88] The instrument has been validated for use by adolescents aged 12 and older.[79]

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

The EuroQoL 5 Dimensions (EQ-5D-5L) is a validated, standardized, generic instrument that is the most widely used preference-based HRQoL questionnaire in cost-effectiveness and health technologies assessment (HTA). [80-82] The measure is a well-established instrument used to measure health states and utilities in various disease areas. The measure contains 5 items that cover mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale. A version of the instrument specifically developed and validated for use by youths aged 12 through 17 years is called the EuroQoL 5 Dimensions—Youth (EQ-5D-Y) will be used for adolescent subjects.

7.8.6. 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 subject depression level. Subjects with clinically significant depression as noted by a PHQ-8 total score ≥15 at Screening must not be enrolled in the study.

7.8.7. 36-Item Short Form Health Survey Version 2 Acute (SF36v2 Acute)

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

7.8.8. Alopecia Areata Resource Utilization (AARU)

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

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

The Work Productivity and Activity Impairment: Alopecia Areata (WPAI: AA) is a validated scale that was developed to measure the effect on work productivity and regular activities during the past 7 days, which has been modified specifically for patients with AA. The WPAI: AA will be completed by adult subjects only. Adolescents aged 12-17 years will not complete this assessment.

7.9. Photography of Alopecia Areata

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

Scalp photographs will be taken at the Screening Visit to verify eligibility (eg, ≥50% hair loss of the scalp). Scalp areas photographed should be recorded in study documents so that the same scalp region(s) will be photographed at all time points as applicable. Photographs of eyelashes and eyebrows will also be taken. Photographs will also be taken at Baseline, Weeks 4, 12, 24, 28, 40, and 48 (or ET) visits. Photographs of affected fingernails may be taken at the investigator's discretion.

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

7.10. Pharmacokinetics

7.10.1. Plasma for Analysis of PF-06651600

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

Blood will be collected at the time points identified in the Schedule of Activities section of the protocol. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. For each blood sample collection, the allowable windows are as follows for time postdose: 0.5 hr (±10 min), 1 hr (±15 min), 2 hr (±20 min) and 3 hr (±30 min). The date and exact time of the sample collection is to be noted on the source document and data collection tool (eg, CRF), as well as the date and time of the previous dose. Samples obtained outside the windows specified in the Schedule of Activities will be considered a protocol deviation.

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

- As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.10.2. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the Investigator site prior to initiation of the study. The central laboratory will provide collection materials and directions for packaging and shipment of samples and will forward samples to the contract analytical laboratory. The contract analytical laboratory will be provided with randomization codes so that only samples in the PF-06651600 treatment groups are assayed. Placebo samples may be assayed in the event of suspected error in subject randomization. Refer to the central lab vendor manual for further information.

7.11. Pharmacodynamics Markers

The pharmacodynamic (PD) samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Depending on sampling and transport constraints, it is possible that not all biomarker samples will be collected in all study regions.

All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. Please consult the laboratory manual(s) for final instructions on sample collection, storage, and shipping requirements. These manual(s) supersede the instructions listed in the applicable protocol sections. Samples that are handled according to the respective manual guidance are considered “per protocol”.

Samples will be analyzed using fit for purpose or validated analytical methods in compliance with Pfizer standard operating procedures.

As part of understanding the pharmacodynamics of the study drug and the disease under study, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and may not be included in the clinical report.

7.11.1. Samples for Interferon Gamma-Induced Protein – 10 (IP-10) Analysis

Blood samples to provide serum for the analysis of IP-10 will be collected into appropriately labeled tubes according to the times outlined in the Schedule of Activities. IP-10 samples will be collected from all subjects unless the exportation of these samples from the country of origin is prohibited by local regulators or IRB/EC decision.

7.11.2. Samples for fluorescence-activated cell sorting (FACS) analysis (T cell, B cell, and NK cell subsets)

Blood samples for the assessment of percent and absolute lymphocyte subsets will be collected and will be analyzed by FACS to identify T cell, B cell, and NK cell subsets according to the times outlined in the Schedule of Activities.

7.11.3. Samples for Immunoglobulins (IgA, IgG, IgM) Analysis

Blood sample for the analysis of immunoglobulin subtypes (IgA, IgG, and IgM) will be collected according to the times outlined in the Schedule of Activities.

7.11.4. Shipment of Pharmacodynamic Samples

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

7.12. Rater Qualifications

Diagnosis of AA must be performed by a qualified dermatologist (board certified or equivalent) who has experience with AA. The assessment of fingernails affected by AA must be performed by a qualified dermatologist (board certified or equivalent). An experienced and qualified physician or healthcare professional may be permitted to perform the clinical evaluations of AA (SALT, ELA, EBA, and CGI-AA). The C-SSRS may be performed by site staff. For all assessments, the rater must be formally delegated to perform this assessment by the PI and receive training (with proper documentation) on the protocol and applicable assessment scales prior to performing these evaluations. To assure consistency and reduce variability, the same rater should assess dermatological clinical evaluations for a given procedure and for an individual subject throughout the study (eg, one rater performs all SALT evaluations throughout the study). The same rater must assess the SALT and CGI-AA for an individual subject. 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. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;

- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;

- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

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

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

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

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

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

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

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

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

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

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

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

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

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

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

8.4.3.2. Exposure during Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

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

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

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

Medication errors include:

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

For further clarification, a medication error is:

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

A medication error is not an inadvertent or intentional missing of a dose or use of extra dose of study medication by a subject who understands dosing instructions. This is a compliance issue. Reporting of compliance issues are described in Section 5.3.

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

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

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

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

8.4.5. Safety Adjudication Committees

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

This section outlines the key planned statistical summaries and analyses for the data collected in this study. Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (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. The SAP will be finalized prior to database lock and breaking the blind for the primary analysis of the B7981015 study.

Section 2 lists the overall study objectives and endpoints; the primary and secondary objectives and endpoints for the overall study reporting and publications are also detailed below in Table 4. Table 5 lists the primary and secondary endpoints of the study organized by known regional requirements.

Table 4. Primary and Secondary Endpoints for Overall Study Reporting and Publications

Alpha (α)	0.05 (2-sided significance level)
Primary Endpoint	Response based on an absolute SALT Score ≤20 at Week 24.
Key Secondary Endpoint	Response based on an absolute SALT Score ≤10 at Week 24.
Secondary Endpoints	• Response based on an absolute SALT Score ≤20 at Week 24 will be used to characterize the exposure response.
	• Response based on an absolute SALT score ≤20 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48. NOTE: Response at Weeks 4, 8, 12, and 18 will be analyzed controlling for Type I error.
	• Response based on an absolute SALT score of ≤10 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48.
	• Response based on a 75% improvement in SALT score from baseline (SALT75) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• Change from baseline in SALT scores at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• Response based on at least a 2-grade improvement or a score of 3 in EBA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• Response based on at least a 2-grade improvement or a score of 3 in ELA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• PGI-C response defined as a PGI-C score of “moderately improved” or “greatly improved” at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.
	• Change from baseline in AAPPO scales at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.

Table 5. Primary and Secondary Endpoints Organized by Known Regional Regulatory Requirements

	For the FDA/PMDA	For the EMA and competent authorities in the VHP countries
Alpha (α) CCI [redacted]	0.00125 (2-sided significance level)	0.01 (2-sided significance level)
Primary Endpoint	Response based on an absolute SALT Score ≤20 at Week 24.	Response based on an absolute SALT Score ≤10 at Week 24.
Key Secondary Endpoint	Not applicable	PGI-C response defined as a PGI-C score of "moderately improved" or "greatly improved" at Week 24.
Secondary Endpoints	• Response based on an absolute SALT Score ≤20 at Week 24 will be used to characterize the exposure response.	• Response based on an absolute SALT Score ≤10 at Week 24 will be used to characterize the exposure response.
	• Response based on an absolute SALT score ≤20 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48. NOTE: Response at Weeks 4, 8, 12, and 18 will be analyzed controlling for Type I error.	• Response based on an absolute SALT score ≤20 at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. NOTE: Response at Week 24 will be analyzed controlling for Type I error.
	• Response based on an absolute SALT score of ≤10 at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. NOTE: Response at Week 24 will be analyzed controlling for Type I error.	• Response based on an absolute SALT score of ≤10 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48. NOTE: Response at Weeks 4, 8, 12, and 18 will be analyzed controlling for Type I error.
	• Response based on a 75% improvement in SALT score from baseline (SALT75) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.	• Response based on a 75% improvement in SALT score from baseline (SALT75) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• Change from baseline in SALT scores at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.	• Change from baseline in SALT scores at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• Response based on at least a 2-grade improvement or a score of 3 in EBA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.	• Response based on at least a 2-grade improvement or a score of 3 in EBA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• Response based on at least a 2-grade improvement or a score of 3 in ELA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.	• Response based on at least a 2-grade improvement or a score of 3 in ELA score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
	• PGI-C response defined as a PGI-C score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.	• PGI-C response defined as a PGI-C score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 34, 40, and 48.
	• Change from baseline in AAPPO scales at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.	• Change from baseline in AAPPO scales at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.
	-	• Change from baseline in the depression subscale score of the HADS at Weeks 4, 8, 12, 24, and 48.

Table 5. Primary and Secondary Endpoints Organized by Known Regional Regulatory Requirements

	For the FDA/PMDA	For the EMA and competent authorities in the VHP countries
	-	• Change from baseline in the anxiety subscale score of the HADS at Weeks 4, 8, 12, 24, and 48.
	-	• Improvement on HADS among subjects with a baseline subscale score indicative of depression who achieved a "normal' subscale score indicative of an absence of depression at Weeks 4, 8, 12, 24, and 48.
	-	• Improvement on HADS among subjects with a baseline subscale score indicative of anxiety who achieved a "normal' subscale score indicative of an absence of anxiety at Weeks 4, 8, 12, 24, and 48.

9.1. Sample Size Determination

The sample size for the study was based on the consideration to have sufficient power to evaluate the primary endpoint. A sample size of 120 subjects per group (for the 200 mg/50 mg once daily (QD), 200 mg/30 mg QD, 50 mg/50 mg QD, or 30 mg/30 mg QD groups) will provide more than 90% power to demonstrate that at least the 200 mg/50 mg group is superior to placebo by a difference of 24% in the proportion of subjects achieving the primary endpoint (SALT ≤20 at Week 24), assuming a placebo response rate of no more than 5%, at $\alpha = 0.05$ (2-sided significance level). This sample size accounts for multiplicity using a closed testing procedure to ensure strong control of Type I error for all comparisons between active treatment groups and placebo. This sample size additionally provides >90% power for the SALT ≤10 at Week 24 endpoint assuming that the 200 mg/50 mg QD group is superior to placebo by a difference of 20% in the proportion of subjects achieving SALT ≤10, assuming a placebo response rate of no more than 5%, at $\alpha = 0.05$ (2-sided significance level). The assumption of the placebo response rate for both SALT ≤20 and SALT ≤10, as well as the treatment difference, was informed by the Week 24 results from the Phase 2a Study B7931005. [92]

Regulatory requirements for a marketing authorization approval CCI [redacted] will require significance at an α more stringent than 0.05, although the exact level of stringency required may vary (ie, 0.00125 is required by the FDA/PMDA for their requested primary endpoint of SALT ≤20, while 0.01 is required by the EMA for their requested primary endpoint of SALT ≤10). The sample size of 120 subjects per group provides power >90% for SALT ≤20 ($\alpha = 0.00125$) and SALT ≤10 ($\alpha = 0.01$).

The 10 mg/10 mg QD group is included to address the secondary objective of characterizing the exposure response. The sample size of 60 subjects for this group was chosen to allow for estimation of the exposure response parameters.

For the EMA and competent authorities in the VHP countries, that request that the PGI-C response at Week 24 be analyzed as a key secondary endpoint, a sample size of 120 subjects per group also provides more than 90% power for PGI-C response assuming a difference of 35% and a placebo response rate of 20%, at $\alpha = 0.05$ (2-sided significance level). The assumptions of the treatment difference and placebo response rate for PGI-C response were based on the Concert CTP-543 Phase 2b Study Week 24 data.[90] Under the above assumptions, the power of the study remains >90% at $\alpha = 0.01$ (EMA required 2-sided significance level).

9.2. Efficacy Analysis

The primary analysis population for efficacy data will be the Full Analysis Set (FAS) defined as all randomized subjects, regardless of whether they received study medication. In the comparison to placebo, the data from the 2 groups F and G up to Week 24 will be pooled to form the placebo group.

9.2.1. Testing Procedure for Multiple Comparisons

This section describes the testing procedure for multiple comparisons. This CCI [redacted] will support submission in several regions with different requirements; therefore, this section is organized into 3 sections: Section 9.2.1.1, Section 9.2.1.2, and Section 9.2.1.3 describe the testing procedure for the overall study, for the FDA/PMDA, and for the EMA and competent authorities in the VHP countries, respectively.

9.2.1.1. Overall Study (Testing Procedure for Multiple Comparisons Incorporating the SALT ≤10 as a Key Secondary Endpoint)

For the overall study the SALT ≤20 response at Week 24 is the primary endpoint and the SALT ≤10 response at Week 24 will be analyzed as a key secondary endpoint. The hypotheses to be tested are that each of the active treatment groups is superior to placebo as measured by the proportion of subjects achieving the primary endpoint and the key secondary endpoint. There are a total of 8 hypotheses to be tested:

- Hypothesis 1 (H1) is to test whether the 200 mg QD/50 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 2 (H2) is to test whether the 50 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 3 (H3) is to test whether the 200 mg QD/30 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 4 (H4) is to test whether the 30 mg QD dose regimen is superior to placebo for the primary endpoint;

- Hypothesis 1p (H1p) is to test whether the 200 mg QD/50 mg QD dose regimen is superior to placebo for the key secondary endpoint;

- Hypothesis 2p (H2p) is to test whether the 50 mg QD dose regimen is superior to placebo for the key secondary endpoint;

- Hypothesis 3p (H3p) is to test whether the 200 mg QD/30 mg QD dose regimen is superior to placebo for the key secondary endpoint;

- Hypothesis 4p (H4p) is to test whether the 30 mg QD dose regimen is superior to placebo for the key secondary endpoint.

The family-wise Type I error will be strongly controlled using a gatekeeping approach as described in the following order and shown in Figure 2. The 10 mg group comparison to placebo is not included in the Type I error controlled procedure, as this group is only included to support the estimation of the exposure response.

- The primary endpoint for 200 mg QD/50 mg QD dose regimen (H1) will be tested at α significance level first. If significant, then the primary endpoint for 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen (H2 and H3) and the key secondary endpoint for 200 mg QD/50 mg QD dose regimen (H1p) will be tested simultaneously. If both the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen are significant, then the 30 mg QD dose regimen will be tested.

- For the primary endpoint, if both the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen are significant at $\alpha/4$ level, or if one of the dose regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is significant at $\alpha/2$ level, both dose regimens will be declared as significant. In this case, the 30 mg QD dose regimen will be tested at $\alpha/2$ level. If only one of the regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is not significant at $\alpha/2$ level, only the one significant at $\alpha/4$ level will be declared as statistically significant. In this case, the testing for the 30 mg QD dose regimen will not proceed.

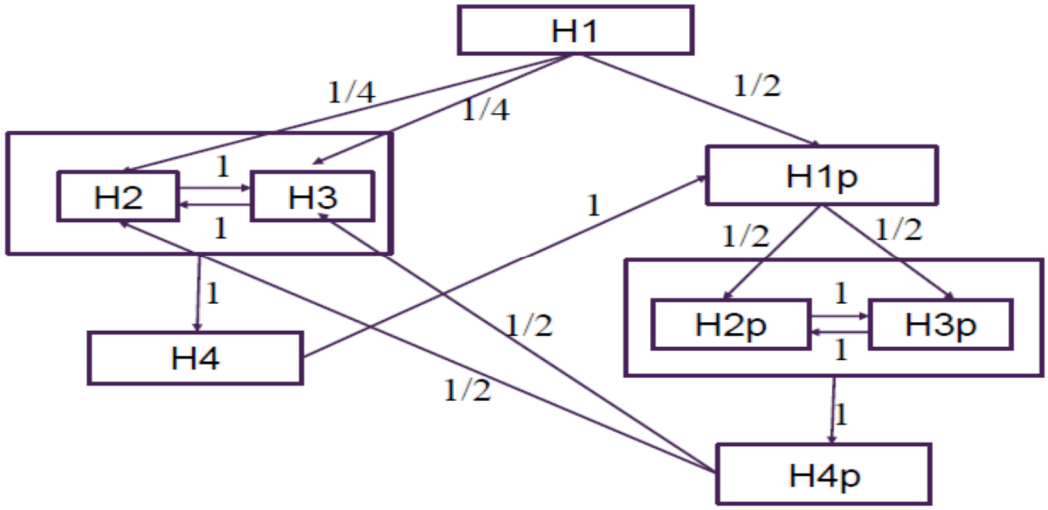
- For the key secondary endpoint, the 200 mg QD/50 mg QD dose regimen will be tested at $\alpha/2$ level first. If significant, then the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen will be tested simultaneously. If both the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen are significant at $\alpha/4$ level, or if one of the dose regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is significant at $\alpha/2$ level, both dose regimens will be declared as significant. In this case, the 30 mg QD dose regimen will be tested at $\alpha/2$ level. If only one of the regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is not significant at $\alpha/2$ level, only the one

significant at α/4 level will be declared as statistically significant. In this case, the testing for the 30 mg QD dose regimen will not proceed.

- If the primary endpoint for the 200 mg QD/50 mg QD dose regimen is significant at α level, and all the remaining hypotheses for the primary endpoint and key secondary endpoint are significant at the overall α/2 level, then all 8 hypotheses will be declared as statistically significant.

- If the primary endpoint for all 4 hypotheses or the primary endpoint for H1 is significant and the key secondary endpoint is significant in all 4 hypotheses, then the α/2 level will be passed to the hypothesis testing for the other hypotheses. In this case, the other hypotheses can be tested at the α level instead of the α/2 level following the same procedures for claiming statistical significance outlined in the bullets above with the exception of the increased α.

Figure 2. Schematic and Graphical Presentation for Multiple Testing Procedure Incorporating a Key Secondary Endpoint



The numbers on each edge indicate the transition rule for the weights on α allocation once a hypothesis is rejected.

The following approach will be used to control the Type I error for SALT ≤20 at earlier time points. For a given dose, if the primary endpoint of SALT ≤20 is declared to be statistically significant based on the testing procedure for the primary endpoint, in order to establish the onset of efficacy as measured by SALT ≤20 at the earliest time point, a step-down approach with SALT ≤20 from Week 24 to earlier time points (order of testing: Weeks 24, 18, 12, 8, and 4) will be used for each time point. Although this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of SALT ≤20 time points within the same dose group.

9.2.1.2. For the FDA/PMDA (Testing Procedure for Multiple Comparisons With no Key Secondary Endpoints)

For the FDA/PMDA, the SALT ≤20 response at Week 24 is the primary endpoint and no secondary endpoints will be analyzed as key secondary. The hypotheses to be tested are that each of the active treatment groups is superior to placebo as measured by the proportion of subjects achieving the primary endpoint. If the hypothesis test is significant at the $\alpha = 0.00125$ level, the active treatment group will be declared to be superior to placebo group in treating patients with moderate to severe AA and the study will meet its primary endpoint.

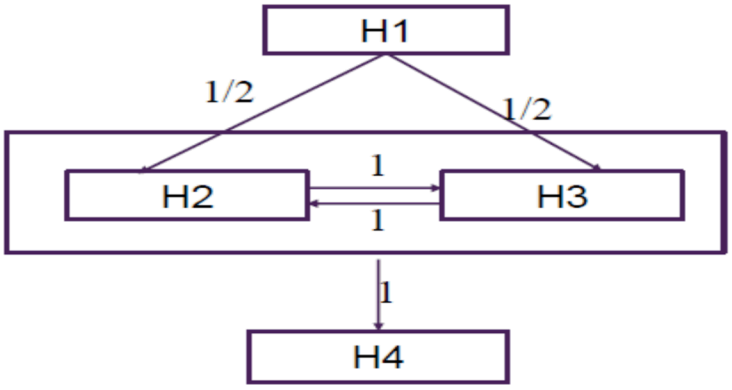
There are a total of 4 hypotheses to be tested.

- Hypothesis 1 (H1) is to test whether the 200 mg QD/50 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 2 (H2) is to test whether the 50 mg QD/50 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 3 (H3) is to test whether the 200 mg QD/30 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 4 (H4) is to test whether the 30 mg QD/30 mg QD dose regimen is superior to placebo for the primary endpoint.

The family-wise Type I error will be strongly controlled using a gate-keeping approach to test these hypotheses in 3 groups. The first group includes H1; the second group includes H2 and H3; and the third group includes H4. The statistical significance of the first hypothesis (H1) will allow simultaneous testing of H2 and H3 using Holm's method.[83] Statistical significance for both H2 and H3 will enable testing the statistical significance for the fourth hypothesis (H4). The 10 mg group comparison to placebo is not included in the Type I error-controlled procedure, as this group is only included to support the estimation of the exposure response.

The grouping of the dose regimens in the test hierarchy was based on the hierarchy of 2 different dose regimens: in the dosing regimens that have a loading dose, the order is 200 mg QD/50 mg QD → 200 mg QD/30 mg QD; in the regimens without a loading dose, the order is 50 mg QD/50 mg QD → 30 mg QD/30 mg QD. The testing strategy proposed will allow simultaneous testing of the 200 mg QD/30 mg QD and the 50 mg QD/50 mg QD dose regimens against placebo given that it is not known which dose regimen will have a better response. Figure 3 shows a schematic of the procedure for testing each of the active treatment groups versus the placebo group for the primary endpoint.

Figure 3. Schematic and Graphical Presentation for Multiple Testing Procedure



The numbers on each edge indicate the transition rule for the weights on α allocation once a hypothesis is rejected.

In the simultaneous testing of H2 and H3, if both the 50 mg QD/50 mg QD and 200 mg QD/30 mg QD regimens are not significant at α/2 level, the test for statistical significance is stopped. If one of the hypotheses for 50 mg QD/50 mg QD and 200 mg QD/30 mg QD regimens is significant at α/2 level and the other hypothesis is significant at α level, this family hypothesis is significant. If one of the hypotheses for 50 mg QD/50 mg QD and 200 mg QD/30 mg QD is significant at α/2 level and the other hypothesis is not significant at α level, only the hypothesis significant at α/2 level will be declared as statistically significant. In this case, the testing for statistical significance for H4 will not proceed.

The following approach will be used to control the Type I error for SALT ≤10 at Week 24 and SALT ≤20 at earlier time points. For a given dose, if SALT ≤20 at Week 24 is declared to be statistically significant based on the testing procedure for the primary endpoint, then SALT ≤10 at Week 24 will be tested at the same significance level as the SALT ≤20 at Week 24 was tested. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the endpoints within the same dose group. For a given dose, if the primary endpoint of SALT ≤20 is declared to be statistically significant based on the testing procedure for the primary endpoint, in order to establish the onset of efficacy as measured by SALT ≤20 at the earliest time point, a step-down approach with SALT ≤20 from Week 24 to earlier time points (order of testing: Weeks 24, 18, 12, 8, and 4) will be used for each time point. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of SALT ≤20 time points within the same dose group.

9.2.1.3. For the EMA and Competent Authorities in the VHP Countries (Testing Procedure for Multiple Comparisons Incorporating the PGI-C Response as a Key Secondary Endpoint)

For the EMA and competent authorities in the VHP countries, the SALT ≤10 response at Week 24 will be the primary endpoint and the PGI-C response at Week 24 will be analyzed as a key secondary endpoint. The hypotheses to be tested at α=0.01 are that each of the active treatment groups is superior to placebo as measured by the proportion of subjects achieving the primary endpoint and the key secondary endpoint. There are a total of 8 hypotheses to be tested.

- Hypothesis 1 (H1) is to test whether the 200 mg QD/50 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 2 (H2) is to test whether the 50 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 3 (H3) is to test whether the 200 mg QD/30 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 4 (H4) is to test whether the 30 mg QD dose regimen is superior to placebo for the primary endpoint;
- Hypothesis 1p (H1p) is to test whether the 200 mg QD/50 mg QD dose regimen is superior to placebo for the key secondary endpoint;
- Hypothesis 2p (H2p) is to test whether the 50 mg QD dose regimen is superior to placebo for the key secondary endpoint;
- Hypothesis 3p (H3p) is to test whether the 200 mg QD/30 mg QD dose regimen is superior to placebo for the key secondary endpoint;
- Hypothesis 4p (H4p) is to test whether the 30 mg QD dose regimen is superior to placebo for the key secondary endpoint.

The family-wise Type I error will be strongly controlled using a gate-keeping approach as described in the following order and shown in Figure 2 in Section 9.2.1.1. The 10 mg group comparison to placebo is not included in the Type I error-controlled procedure, as this group is only included to support the estimation of the exposure response.

- The primary endpoint for 200 mg QD/50 mg QD dose regimen (H1) will be tested at α significance level first. If significant, then the primary endpoint for 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen (H2 and H3) and the key secondary endpoint for 200 mg QD/50 mg QD dose regimen (H1p) will be tested simultaneously. If both the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen are significant, then the 30 mg QD dose regimen will be tested.

- For the primary endpoint, if both the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen are significant at $\alpha/4$ level, or if one of the dose regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is significant at $\alpha/2$ level, both dose regimens will be declared as significant. In this case, the 30 mg QD dose regimen will be tested at $\alpha/2$ level. If only one of the regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is not significant at $\alpha\alpha/2$ level, only the one significant at $\alpha/4$ level will be declared as statistically significant. In this case, the testing for the 30 mg QD dose regimen will not proceed.

- For the key secondary endpoint, the 200 mg QD/50 mg QD dose regimen will be tested at $\alpha/2$ level first. If significant, then the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen will be tested simultaneously. If both the 50 mg QD dose regimen and the 200 mg QD/30 mg QD dose regimen are significant at $\alpha/4$ level, or if one of the dose regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is significant at $\alpha/2$ level, both dose regimens will be declared as significant. In this case, the 30 mg QD dose regimen will be tested at $\alpha/2$ level. If only one of the regimens (50 mg QD dose regimen or 200 mg QD/30 mg QD dose regimen) is significant at $\alpha/4$ level and the other is not significant at $\alpha/2$ level, only the one significant at $\alpha/4$ level will be declared as statistically significant. In this case, the testing for the 30 mg QD dose regimen will not proceed.

- If the primary endpoint for the 200 mg QD/50 mg QD dose regimen is significant at α level, and all the remaining hypotheses for the primary endpoint and key secondary endpoint are significant at the overall $\alpha/2$ level, then all 8 hypotheses will be declared as statistically significant.

- If the primary endpoint for all 4 hypotheses or the primary endpoint for H1 is significant and the key secondary endpoint is significant in all 4 hypotheses, then the $\alpha/2$ level will be passed to the hypothesis testing for the other hypotheses. In this case, the other hypotheses can be tested at the α level instead of the $\alpha/2$ level following the same procedures for claiming statistical significance outlined in the bullets above with the exception of the increased α.

For the EMA and competent authorities in the VHP countries, for a given dose, if SALT $\leq$10 at Week 24 is declared to be statistically significant based on the testing procedure for the primary endpoint incorporating the key secondary endpoint, then SALT $\leq$20 at Week 24 will be tested at the same significance level as SALT $\leq$10 at Week 24 was tested. Although this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the endpoints within the same dose group. For a given dose, if the primary endpoint of SALT $\leq$10 is declared to be statistically significant based on the testing procedure for the primary endpoint incorporating the key secondary endpoint, in order to establish the onset of efficacy as measured by SALT $\leq$10 at the earliest time point, a step-down approach with SALT $\leq$10 from Week 24 to earlier time

points (order of testing: Weeks 24, 18, 12, 8, and 4) will be used for each time point. Although this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of SALT ≤10 time points within the same dose group.

9.2.2. Analysis of the Primary and Key Secondary Endpoints

The analyses of primary and key secondary endpoints are described separately for the overall study and for specific regulatory regions in order to address differences in advice received from some regulatory agencies.

9.2.2.1. For the Overall Study and the FDA/PMDA (Analysis of the Primary and Key Secondary Endpoints)

For the overall study and for the FDA/PMDA, the SALT ≤20 response at Week 24 is the primary endpoint. The SALT ≤10 response at Week 24 will be analyzed as a key secondary endpoint for the overall study but not for the FDA/PMDA. The testing procedures are described in Section 9.2.1.1 and Section 9.2.1.2, and the planned analysis of the primary endpoint are described in Table 6.

Table 6. Statistical Methods for the Analysis of the Primary Endpoint for the Overall Study, and for the FDA/PMDA

Analysis #	Analysis Designation	Statistical Method	Approach for missing data due to COVID-19	Approach for missing data due to other reasons
1	Primary	MN	Exclude missing	Consider missing as non-responders
2	Supplementary	GLMM	MAR	MAR
2a	Supplementary	GLMM/ Tipping point	MNAR	MNAR
3	Supplementary	MN	Consider missing as non-responders	Consider missing as non-responders

Abbreviations: GLMM = generalized linear mixed model; MN = Miettinen and Nurminen; MAR = Missing at random; MNAR = Missing not at random

In the primary analysis for the overall study, and for the FDA/PMDA, the primary endpoint will be analyzed by the MN method[84] for the difference in the proportion of responders between each active treatment group and placebo. Subjects with missing SALT score at Week 24 due to COVID-19 related reasons will be excluded from the analysis at that time point, whereas missing data due to other reasons will be counted as non-responders at that time point (Analysis 1). As a supplementary analysis to assess the impact of COVID-19-related missing data on the results of the primary analysis, the analysis of the primary endpoint will be repeated with all missing data considered as non-responders regardless of the reason for missingness (Analysis 3).

As a supplementary analysis a GLMM for the longitudinal binary data of SALT ≤20 response over time up to Week 24 will be conducted (Analysis 2) to evaluate the impact of the missing data approach to the primary conclusion. In this analysis, two different missing mechanisms will be assumed: MAR and MNAR. A tipping point analysis will be conducted under MNAR (Analysis 2a).

The key secondary endpoint for the overall study (SALT ≤10 response at Week 24) will be analyzed using the same approach as Analysis 1. Analysis 4 described in Table 7 will also be conducted for this endpoint as supplementary.

9.2.2.2. For the EMA and Competent Authorities in the VHP Countries (Analysis of the Primary and Key Secondary Endpoints)

For the EMA and competent authorities in the VHP countries, the SALT ≤10 response at Week 24 will be the primary endpoint and the PGI-C response at Week 24 will be analyzed as a key secondary endpoint. The testing procedures are described in Section 9.2.1.3, and the planned analysis of the primary endpoint are described in Table 7.

Table 7. Statistical Methods for the Analysis of the Primary Endpoint for the EMA and Competent Authorities in the VHP Countries

Analysis #	Analysis Designation	Statistical Method	Approach for missing data due to COVID-19	Approach for missing data due to other reasons
4	Primary	GLMM	MAR	Consider missing as non-responders
4a	Supplementary	GLMM/ Tipping point	MNAR	Consider missing as non-responders
1	Supplementary	MN	Exclude missing	Consider missing as non-responders
3	Supplementary	MN	Consider missing as non-responders	Consider missing as non-responders

Abbreviations: GLMM = generalized linear mixed model; MN = Miettinen and Nurminen; MAR = Missing at random; MNAR = Missing not at random

The primary analysis of the primary endpoint for the EMA and competent authorities in the VHP countries (Analysis 4) will be conducted using a GLMM model for the longitudinal binary data of SALT ≤10 response over time up to Week 24, assuming a missing mechanism of MAR for missing data due to COVID-19. Missing data due to reasons not related to COVID-19 will be assumed as non-responders. The key secondary endpoint will also be analyzed using this approach.

As a supplementary analysis, imputations will be implemented under the framework of the same GLMM model as above, using a tipping point analysis (Analysis 4a). For this analysis,

the assumption of the missing mechanism for this analysis will be MNAR for cases of missing data due to COVID-19, and missing data due to other reasons will be considered as non-responders.

Additional supplementary analyses will use the MN method to estimate 95% CIs and p-values for the differences in the proportions of response between each active treatment group and placebo. In Analysis 1 missing data due to COVID-19 will be excluded from the analysis, whereas missing data due to other reasons will be considered as non-responders. In Analysis 3, all missing data will be considered as non-responders, regardless of the reason for missingness.

9.2.2.3. Per-Protocol Analysis (Analysis of the Primary and Key Secondary Endpoints)

In addition to the analyses described in Section 9.2.2.1 and in Section 9.2.2.2, the primary analyses of the primary endpoints and key secondary endpoints will also be performed in the Per Protocol Analysis Set (PPAS), defined as all randomized subjects who do not have any major protocol deviations related to inclusion/exclusion criteria, compliance with investigational product or any other major protocol deviation that might affect the efficacy data at Week 24.

The following protocol deviations will be evaluated for each subject prior to unblinding to determine if a subject should be excluded from the PPAS:

1. Subject did not meet the following inclusion criteria for hair loss due to AA at Screening or Day 1:
    a. Clinical diagnosis of AA with no other known etiology of hair loss, including no known androgenetic alopecia
    b. ≥50% scalp hair loss
    c. Current episode of hair loss ≤10 years duration at time of Screening
    d. No evidence of terminal scalp hair regrowth within 6 months at both the screening and baseline visits
2. Subject met one of the following exclusion criteria regarding medical history diagnoses:
    a. Another scalp disease which could impact hair loss assessments
    b. Active systemic disease which can cause hair loss
3. Subjects who were randomized but never received study drug
4. Prior to the date of the Week 24 visit, subject had a dosing interruption of ≥6 weeks for any reason
5. Prior to the date of the Week 24 visit, subject used a prior or concomitant prohibited medication that could potentially impact efficacy data at Week 24

6. Week 24 SALT assessment was impacted in one of the following ways:
    a. Visit/assessment was not performed
    b. Assessment was not performed properly (including subject had a shaved head)
7. Subjects with other major protocol deviations not listed above that, in the opinion of the sponsor study team, could potentially impact efficacy data at Week 24

The subjects excluded from this analysis set will be determined and documented before the study is unblinded.

9.2.3. Analysis of Secondary Endpoints

For all regions, analyses of secondary endpoints that are not α controlled will use the approach outlined below.

Secondary endpoints that are binary variables will be analyzed using the same approach as Analysis 1 in Table 6.

For continuous endpoints, a mixed-effects model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, visit, treatment-by-visit interaction, and relevant baseline value when modeling change from baseline. Within the framework of MMRM, the treatment difference will be tested at each time point.

All secondary endpoints will be evaluated at the 5% level of significance, without adjustment for multiple comparisons.

Details on the analysis of individual secondary endpoints will be provided in the SAP.

9.2.3.1. Analysis of Exposure-Response

To characterize the exposure response (dose or average steady state drug concentration [C_{avg}]) in achieving the primary endpoint, a Bayesian three-parameter maximum effect attributable to the drug (E_{max}) exposure-response model will be used as the primary analysis approach to characterize the exposure response relationship. The response function will be the log odds (logit) of the proportion of subjects achieving the primary endpoint. In modeling the exposure response, the effect of loading dose will be included as fixed factor in the model. Model-based estimation of treatment effect for each dose or associated C_{avg} compared to placebo will be presented with 95% CIs. The model will be described in detail in the SAP.

9.2.4. Analysis of Other Endpoints

Analysis of other endpoints will be conducted using descriptive statistics.

9.2.5. Subgroup Analyses

Summary statistics for SALT ≤20 response at Week 24, SALT ≤10 response at Week 24, and PGI-C response at Week 24 will be presented by subgroups, including but not limited to:

- Age (years) at baseline (12-17, ≥18);

- Age (years) at baseline (12-17, 18-44, 45-64, ≥65);
- Body Mass Index (BMI) at baseline (<median, ≥median);
- Weight at baseline (<median, ≥median);
- Gender (male, female);
- Race (White, Black, Asian, other);
- Region of enrollment (North America, Europe, Asia, Rest of World)

Region	Countries
North America	Canada, United States
Europe	Czech Republic, Germany, Hungary, Poland, Russia, Spain, United Kingdom
Asia	China, Japan, South Korea, Taiwan
Rest of World	Australia, Argentina, Chile, Colombia, Mexico

- Baseline disease severity (AT/AU, non AT/AU);
- AA duration since onset of disease (years) (<median, ≥median);
- AA duration since onset of current episode (years) (<median, ≥median);
- Prior pharmacological treatment for AA.

Estimates of the response rates for each dose compared to the placebo group and their 95% confidence interval (CI) based on MN method will be presented for each defined category of each subgroup. No p-values will be presented.

The primary purpose of the subgroup analyses is to check for consistency of key efficacy results across subgroups. No inferences will be made within subgroups. These analyses may also be performed on selected country and/or region subpopulation sets in order to meet country/region specific regulatory requirements.

9.3. Pharmacokinetic Analysis during the Treatment Period

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

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

9.4. Pharmacokinetic/Pharmacodynamic Early Unblinding

Early unblinding for PK/PD modeling purposes is planned when ≥90% of subjects have reached 24 weeks post-randomization (or discontinued prior to the Week 24 visit). Unblinding will be limited to the PK/PD analysts and programmers listed on the early unblinding for PK/PD form in accordance with applicable Pfizer standard operating

procedures for releasing randomization codes, early unblinding and breaking the study blind. These data programmers and analysts will not serve on the B7981015 study team after the PK/PD early unblinding.

These PK/PD data analysts and programmers will be unblinded early to build the PK and concentration/response models for study readout. Information, such as drug concentration, that may unblind the study will not be reported to investigator sites or other Pfizer personnel, who will all remain blinded. There will be no impact on B7981015 study conduct, analysis, or reporting based on the early unblinding of the PK/PD data. The results of these analyses will be reported in a separate pharmacometrics analysis report.

9.5. Safety Analysis

The safety data will be summarized in accordance with Pfizer Data Standards. All subjects who receive investigational product (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety data analysis for the study includes:

- Incidence and severity of AEs;
- Safety events that trigger withdrawal of subject from study;
- Incidence of serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials;
- Change from baseline in vital signs;
- Incidence of adjudicated safety events (eg, opportunistic infections, cardiovascular events, and malignancy);
- Safety laboratory tests will be summarized according to Pfizer Standards.

9.6. Exploratory Pharmacodynamic Analysis

Exploratory biomarkers will be listed and summarized by visit and change from baseline for these endpoints will also be summarized at specific time points as reported in the Schedule of Activities.

Appropriate regression models may be used to look at association between these endpoints and any covariates of clinical interest.

9.7. Interim Analysis

The study may be unblinded for Sponsor internal decision-making purposes when ≥ 90% of subjects have reached 24 weeks post-randomization (or discontinued prior to the Week 24 visit), and dissemination of these results will be limited to the unblinded reporting team and Sponsor management. The sponsor personnel who are unblinded will be separate from the study team. The sponsor will still maintain the blind for study team members who will be

involved in daily study conduct, study management, safety and data monitoring through the completion of the study. Investigators and subjects will remain blinded. There will be no impact on B7981015 study conduct, analysis, or reporting.

9.8. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

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

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

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

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

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

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, 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.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s), or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit in the Schedule of Activities. The end of the study is defined as the date of the last visit of the last participant in the study.

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in 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 European Union (EU) requirements.

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Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the 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, clinical study reports (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 contributes 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.

15.2. Publications by Investigators

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

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

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

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

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

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

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

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96. B7981032. A Phase 3 Open-Label, Multi-Center, Long-Term Study Investigating the Safety and Efficacy of PF-06651600 in Adult and Adolescent Participants With Alopecia Areata.

Appendix 1. Abbreviations

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

Abbreviation	Term
5-ARIs	5α-reductase inhibitors
AA	Alopecia areata
AE	Adverse event
AAPPO	Alopecia areata patient priority outcomes
AARU	Alopecia areata resource utilization
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	Alopecia Totalis
ATP	Adenosine triphosphate
AU	Alopecia Universalis
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the plasma concentration time curve from time zero to infinity
BAEP	Brainstem auditory evoked potentials
BBS	Biospecimen Banking System
BCG	Bacille Calmette Guérin
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BSEP	Bile salt export pump
C_{avg}	Average steady state drug concentration
CFB	Change from baseline
CFP-10	Culture filtrate protein 10 kiloDalton
CGI-AA	Clinician Global Impression – Alopecia Areata
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSA	Clinical study agreement
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
CSR	Clinical study report
CT	Clinical Trial
CTA	Clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Term
CYP	Cytochrome P450
CYP3A	Cytochrome P450 isoenzyme 3A
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DNCB	1-chloro-2,4-dinitrobenzene
DPCP	Diphenylcyclopropenone
DU	Dispensable unit
EBA	Eyebrow Assessment
EBV	Epstein Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
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
E_{max}	Maximum effect attributable to the drug
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQoL 5 dimensions
EQ-5D-Y	EuroQoL 5 Dimensions—Youth
ESAT-6	Early secreted antigenic target of 6 kiloDalton
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS-TBNK	Fluorescence-activated cell sorting for T-cells, B-cells, and natural killer (NK) cells
FAS	Full analysis set
FDA	United States Food and Drug Administration
FSH	Follicle-stimulating hormone
F/U	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLMM	Generalized linear mixed model
GST	Glutathione S transferase
H1	Hypothesis 1
HADS	Hospital Anxiety and Depression scale
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody

Abbreviation	Term
HBsAg	Hepatitis B surface antigen
HBVDNA	Hepatitis B viral deoxyribonucleic acid
HCRU	Healthcare resource utilization
HCVAb	Hepatitis C antibody
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HsCRP	High-sensitivity C-reactive protein
HSV1	Herpes simplex virus type 1
HSV2	Herpes simplex virus type 2
HTA	Health technologies assessment
IB	Investigator's brochure
IC_{50}	Inhibitory concentration 50%
ICH	International Council for Harmonisation
ID	Identification
IFN	Interferon
Ig	Immunoglobulin
IGA-AA	Investigator's global assessment of alopecia areata
IL	Interleukin
IND	Investigational new drug application
INR	International normalized ratio
IP	Investigational product
IP-10	Interferon gamma-induced protein 10
IRB	Institutional review board
IRC	Internal review committee
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWR	Interactive web response
JAK	Janus kinase
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LFT	Liver function test
LOAEL	Lowest observed adverse effect level
Logit	Log odds
LSLV	Last subject last visit
MAR	Missing at random
MATE	Multi-drug and toxic compound extrusion
MCS	Mental component score
MDR	Multi-drug resistance
MMF	Mycophenolate mofetil
MMR	Measles, mumps, rubella
MMRM	Mixed-effect model with repeated measures

Abbreviation	Term
MN	Miettinen and Nurminen
mNAPSI	Modified nail psoriasis severity index
MNAR	Missing not at random
MnB	Meningitidis serogroup B
MRI	Magnetic resonance imaging
MTX	Methotrexate
N/A	Not applicable
NK	Natural killer
NOAEL	No observed adverse effect level
NRS	Numerical rating scale
OAT	Organic anion transporting
OATP1B1	Organic anion transporting polypeptide 1B1
OCT	Organic cation transporter
PCD	Primary completion date
PD	Pharmacodynamic(s)
PGI-C	Patient's global impression of change
P-gp	P-glycoprotein
PGx	Pharmacogenomics(s)
PHQ-8	Patient health questionnaire – 8 items
PI	Principal investigator
PK	Pharmacokinetic
PMDA	Japan Pharmaceuticals and Medical Devices Agency
PPAS	Per Protocol Analysis Set
PPD	Purified protein derivative
PRO	Patient reported outcome
P-Sat	Patient Satisfaction with Hair Growth
PT	Prothrombin time
PUVA	Psoralen ultraviolet A
QD	Once daily
QFT-G	QuantiFERON®-TB Gold
QoL	Quality of life
QT interval	Time from the beginning of the QRS complex to the end of the T wave
QTc_F	QT corrected using Fridericia's correction factor
QFT-G test	QuantiFERON®-TB Gold In Tube test
RA	Rheumatoid arthritis
R_{ac}	Accumulation ratio
RNA	Ribonucleic acid
SADBE	Squaric acid dibutylester
SAE	Serious adverse event
SALT	Severity of alopecia tool
SALT50	50% improvement in SALT score from baseline
SALT75	75% improvement in SALT score from baseline
SAP	Statistical analysis plan

Abbreviation	Term
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SDAI	Simple disease activity index
SF-36v2 Acute	36-Item Short Form Health Survey version 2 Acute
SOC	System organ class
SOP	Standard operating procedure
SRSD	Single reference safety document
STAT	Signal transducer and activator of transcription
$t_{1/2}$	Half-life
TB	Tuberculosis
TBili	Total bilirubin
TdP	Torsades de pointes
TEAE	Treatment-emergent adverse event
TEC	Tyrosine kinase expressed in hepatocellular carcinoma
TH1	Type 1 helper
T_{max}	Time after administration of a drug when the maximum plasma concentration is reached
T-Spot test	T-SPOT®.*TB* test
TYK2	Tyrosine kinase 2
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
URI	Upper respiratory infection
US	United States
UVB	Ultraviolet B
VHP	Voluntary Harmonisation Procedure
VZV	Varicella-zoster virus
VZV IgG Ab	Varicella-zoster virus immunoglobulin G antibody
WOCBP	Woman of childbearing potential
WPAI:AA	Work productivity and activity impairment: alopecia areata

Appendix 2. Hepatitis B Testing Algorithm and Full Eligibility Criteria

All subjects will undergo screening for hepatitis B for eligibility (See Appendix 5.1 for Japan-specific requirements).

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

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

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

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

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

Appendix 3. Guidelines for Subject Safety Monitoring and Discontinuation

These guidelines for subject safety monitoring and discontinuation are to be applied to all subjects in study B7981015. Additional individual subject monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Appendix 3.1. Monitoring

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

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

Laboratory Variable	Laboratory Value	Re-testing Timeframe[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) OR Decrease of ≥2.0 g/dL from baseline	Within 1 week
Platelet count	<100,000/mm^3 (<100.0 × 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 8.4.2 for potential cases of drug-induced liver injury.	Within 48 hours
Alanine aminotransferase	See Section 8.4.2 for potential cases of drug-induced liver injury.	Within 48 hours
Total bilirubin	See Section 8.4.2 for potential cases of drug-induced liver injury.	Within 48 hours

a. Based on awareness of the abnormal results.
b. Subjects 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 subject with creatine kinase >10 × ULN.

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

Appendix 3.2. Discontinuation

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

Adverse Events:

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

ECG Findings:

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

Investigational Product Interruptions:

- Subjects interrupting investigational product for more than 10 days between visits 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 associated re-testing timeframes for laboratory abnormalities in Appendix 3.1:

- 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: Subjects 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.

  NOTE: In addition to re-testing creatine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any subject with creatine kinase >10 × ULN.

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

  - >3 times the upper limit of normal with at least one total bilirubin value >2 times the upper limit of normal;

  - >3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);

  - Two sequential AST or ALT elevations >5 times the upper limit of normal, 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 subjects confirmed as pregnant during the study (see Section 8.4.3.1).

Prohibited Medications:

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

Suicidal Ideation:

- Subjects with a "yes" answer on items 4, 5, or on any question in the suicidal behavior section of the C-SSRS must be discontinued. The subject must be referred to a mental health professional for appropriate evaluation and treatment. If the subject cannot be seen by a mental health professional within 24 hours, then the subject should be sent to a local emergency room for psychiatric assessment.

Discontinuation/End of Treatment Monitoring:

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

Appendix 4. Prohibited and Permitted Concomitant CYP3A Inducers and Substrates

Please note that this list addresses only CYP3A inducers and CYP3A substrates. Other prohibited medications for this trial are listed in Section 5.8.2. Refer to Section 5.8.1 for additional information regarding permitted medications for this trial, including CYP3A inhibitors.

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

Appendix 4.1. Prohibited Concomitant CYP3A Inducers and Substrates

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

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

Appendix 4.2. Permitted Concomitant CYP3A Substrates

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

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

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

Appendix 5. Country-specific Requirements

Appendix 5.1. Japan-Specific Requirements for Hepatitis B Testing

1. At screening, HBsAg, HBcAb, and HBsAb will be tested for all subjects in Japan:

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

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

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

    d. If HBsAg is negative, HBcAb is negative, HBsAb is positive, and prior HBV vaccination is unequivocally documented, the subject is eligible for the study and does not require HBVDNA monitoring during the study.

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

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

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

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

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

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

Appendix 6. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer. NOTE: Any deviations from the Schedule of Activities or the protocol (eg, missed or partially completed procedures or assessments) must be reported to the Sponsor in a timely manner and will be reported by the Sponsor as a protocol deviation.

Procedures which are missed due to COVID-19 disruptions 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).

Appendix 6.1. Eligibility

While severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) testing is not mandated for this study, local clinical practice standards for testing should be followed. A subject 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. Subjects with active infections are excluded from study participation per Exclusion #16. When the infection resolves, the patient may be considered for re-screening. In addition, the following criteria apply:

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

- The subject must meet eligibility criteria for the study.

- It must be anticipated that the subject will be able to have the Week 2 and Week 4 safety laboratory tests collected/performed at the study site or an alternative clinical laboratory facility according to the windows in Appendix 6.3

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

Appendix 6.2. 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 subjects at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess subject 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 subject 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.

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 subject is adhering to the contraception method(s) required in the protocol Section 4.3.1. Refer to Section 7.2 of the protocol and Appendix 6.3 regarding pregnancy tests.

For premenarchal female subjects: Check for initiation of menarche.

Collection of updated audiological history (Part 1 in the Audiometry Study Guide Worksheet for Post Day 1 visits) at visits requiring audiological evaluation.

Body temperature and collection method (eg, oral, tympanic, axillary), pulse rate, and respiratory rate (measured by study subject/caregiver).

Administration of the C-SSRS performed by a qualified rater. Per Section 7.7.1, 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 subject 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 subject.

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

Appendix 6.3. Alternative Facilities for Safety Assessments

Laboratory Testing

With the exceptions noted in Appendix 6.1 for Screening and Day 1, if a study subject 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 subject's home per Appendix 6.5. The following safety laboratory evaluations may be performed at a local laboratory or in the subject's home:

Hematology;

Serum chemistry;

Fasting lipid panel;

Urinalysis;

Pregnancy testing (for WOCBP);

Refer to the Schedule of Activities for visits at which these tests are required and to Section 7.5.7 for additional details regarding these tests.

If it is not possible for the subject to have the above tests completed within the visit window specified in the Schedule of Activities, an extended window may be allowed to collect samples for these laboratory tests, provided that the investigator has performed the remote visit as described above, assessed each case, and determined that it would not increase risk to a subject. The extended windows for laboratory sample collection for each study visit are noted in Table 8. 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 subject 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 must be filed in the subject's source documents/medical records. Relevant data from the local laboratory report must be recorded on the CRF.

Special attention should be paid to ensure that laboratory results are checked against the Guidelines for Subject Safety Monitoring and Discontinuation in Appendix 3 and that required follow-up is performed as applicable.

If a subject 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 subject 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 subject (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 subject.** The pregnancy test outcome must be documented in the subject's source documents/medical records and relevant data recorded on the CRF. Confirm that the subject is adhering to the contraception method(s) required in the protocol.

NOTE: Pregnancy testing (for WOCBP) between the Week 40 and 48 visits (at approximately Week 44) and study site contact with subjects to obtain pregnancy test results is required for WOCBP in VHP countries outlined in the Schedule of Activities and Section 7.2.

Table 8. Windows for Remote Visits and Laboratory Sample Collections if Required Due to Disruptions from Public Emergencies

Visit (Day in Study)	Remote Visit Window (Day in Study)[a]	Lab Collection Window (Day in Study)[b]
Week 2 (Day 15)	±3 days (Day 12-18)	±3 days (Day 12-18)
Week 4 (Day 29)	±3 days (Day 26-32)	-3/ +7 days (Day 26-36)
Week 8 (Day 57)	±7 days (Day 50-64)	-7/+14 days (Day 50-71)
Week 12 (Day 85)	±7 days (Day 82-88)	-7/+21 days (Day 82-106)
Week 18 (Day 127)	±7 days (Day 120-134)	-7/+21 days (Day 120-148)
Week 24 (Day 169)	±7 days (Day 162-176)	±7 days (Day 162-176)
Week 26 (Day 183)	±3 days (Day 180-186)	±3 days (Day 180-186)
Week 28 (Day 197)	±3 days (Day 194-200)	-3/+21 days (Day 194-218)
Week 34 (Day 239)	±7 days (Day 232-246)	-7/+21 days (Day 232-260)
Week 40 (Day 281)	±7 days (Day 274-288)	-7/+30 days (Day 274-311)
Week 48 (Day 337)[c]	±7 days (Day 330-344)	-7/+30 days (Day 330-367)

a. These are the same as the windows in the protocol Schedule of Activities.
b. Laboratory results must be received and reviewed by the investigator within 14 days after they are collected to determine eligibility to continue dosing. In addition, laboratory test results from the previous visit must be available and reviewed by the investigator prior to shipping investigational product at the current visit.
c. If subject is rolling over into B7981032, labs must be collected prior to enrollment in B7981032.

Electrocardiograms

If the subject is unable to visit the study site for an ECG after Day 1, the subject may visit an alternative facility to have the ECG performed according to the guidelines in Section 7.5.4. Qualified study site personnel must order, receive, and review results.

Audiological Evaluation

At visits after Screening which require audiological evaluation, if the subject is unable to visit the study site or designated ancillary center for audiological evaluation, the audiological history (Part 1 in the Audiometry Study Guide Worksheet for Post Day 1 visits) must be collected during the remote visit per Appendix 6.2 (or during the home health visit per Appendix 6.5). The audiological evaluation must be performed per Section 7.5.5 at the next available opportunity, even if outside of a protocol-specified visit window.

Appendix 6.4. Investigational Product

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

Investigational product may be shipped by courier to study subjects if permitted by local regulations and in accordance with storage and transportation requirements for the investigational product. Pfizer does not permit the shipment of investigational product by mail. The tracking record of shipments and the chain of custody of investigational product must be kept in the subject'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 investigational product, written consent must be documented in the informed consent document prior to shipping investigational product. If a third-party courier engaged by Pfizer or Pfizer's CRO **is not used** for shipping the investigational product, consent must be verbally obtained (or per local guidelines/regulations) and documented in site's source documents prior to shipping investigational product.

Prior to shipping investigational product to a subject, 1) consent must be obtained and documented as described above, 2) all required safety information listed in Appendix 6.2 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.

Investigational product cannot be shipped to the subject 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 subject to continue investigational product. Refer to Section 5.5 regarding temporary withholding of investigational product.

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

The amount of investigational product 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 investigational product to extend the visit window is not permitted.

Subjects should continue taking the current supply of investigational product until the new supply is received (unless temporary withholding of investigational product is required).

Dosing logs should be shipped with the investigational product.

Study sites should follow up with the subject once the investigational product is received by the subject to review when to start using the new blister cards, the dosing instructions, and completion of the dosing logs.

Subjects should be instructed not to re-use or dispose of any blister cards dispensed at a previous visit.

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

Appendix 6.5. Home Health Visits

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

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

The following may be performed during a home health 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.
- 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 subject is adhering to the contraception method(s) required in the protocol Section 4.3.1. Refer to Section 7.2 of the protocol and Appendix 6.3 regarding pregnancy tests.

For premenarchal female subjects: Check for initiation of menarche.

Collection of updated audiological history (Part 1 in the Audiometry Study Guide Worksheet for Post Day 1 visits) at visits requiring audiological evaluation.

Body temperature and collection method (eg, oral, tympanic, axillary), pulse rate, and respiratory rate (measured by study subject/caregiver).

ECG per Section 7.5.4.

Hematology.

Serum chemistry.

Fasting lipid panel.

Urinalysis.

Pregnancy testing (for WOCBP).

Physical examination.

Appendix 6.6. Adverse Events and Serious Adverse Events

If a subject 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 subject 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 subject must be permanently discontinued from investigational product per Appendix 3.2 of the protocol.

Appendix 6.7. Efficacy Assessments

Efficacy assessments listed in Section 7.6 and Section 7.8 are only to be collected during on-site visits. This includes SALT, ELA, EBA, fingernail assessment, CGI-AA, and all patient reported outcomes.