Protocol B7981032 Vaccine Sub-Study

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

Statistical Analysis Plan (SAP)

Version: 2.0

Date: 20 Jun 2023

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Major Changes in SAP Amendments

Version/Date	Associated Protocol	Rationale	Specific Changes
1/ 08 Jul 2021	Protocol Amendment 5 23 Apr 2021, Appendix 10	This is the first version (V1.0) of the Statistical Analysis Plan (SAP) for the Vaccine Sub-Study of Study B7981032	N/A
2/ 20 Jun 2023	Protocol Amendment 6 28 Mar 2022, Appendix 10	SAP was amended to incorporate changes made to the protocol amendment	• In Section 2.2, "… before or at Month 32 …" was updated to "… before or at Month 56 …".
		For clarification purposes	• In Table 3 for "Physical Examination", "for Day 30" was updated to "For Month 1". • Section 3.4 was revised to clarify the definition of baseline values. • Section 3.5.1 Safety Endpoints Adverse Events and Section 6.3.1 Summaries of Adverse Events were revised to further clarify the risk period for the summarization of adverse events. • Section 5.2 was revised to clarify the natural logarithm (also in Sections 6.2.1.4, 6.2.1.5, 6.2.2.3) was adopted and to include the approach to handle geometric means of GMT, GMC and fold increase when immunogenicity data is below LLOQ. • Section 5.3 was revised to include the approach used to handle missing values when immunogenicity data is recorded as ND or IND. • Sections 6.2.1.4, 6.2.2.1 and 6.2.2.2 were revised to provide further clarification on the summaries for secondary endpoints. • Section 6.3.2 was revised to specify the reporting summaries. • In Section 6.5.3, "Exposure" was updated to "The study treatment exposure". • Appendix 1. Definition of analysis visit window for Month 1 was revised to reflect the ongoing nature of the parent study B7981032.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in the Vaccine Sub-Study of study B7981032. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

The study objectives and corresponding endpoints are listed below in Table 2.

Table 2. Study Objectives and Endpoints

Primary Objective:	**Primary Endpoints:**
Evaluate immune responses to Tdap vaccinations in AA participants treated with PF-06651600.	• Proportion of participants achieving a booster response, defined as 1) ≥4-fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the pre-vaccination concentration was ≤2.7 IU/mL; 2) ≥2-fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the pre-vaccination concentration was >2.7 IU/mL.
Secondary Objectives:	**Secondary Endpoints:**
Evaluate immune response to meningococcal ACWY vaccination in AA participants treated with PF-06651600.	• Proportion of participants achieving ≥1:8 human serum bactericidal activity (hSBA) (in participants with undetectable pre-vaccination assay titers) at Month 1 post-vaccination for serogroup C.
Evaluate immune responses to Tdap and meningococcal ACWY vaccinations based on other vaccine response endpoints in AA participants treated with PF-06651600.	Tdap vaccination: • Proportion of participants with anti-tetanus antibody level ≥1.0 IU/mL on Month 1. • Proportion of participants with anti-tetanus antibody level ≥0.1 IU/mL on Month 1. • Proportion of participants with ≥4x increase in anti-tetanus antibody level from baseline. • Fold increase in anti-tetanus levels above baseline values at Month 1. • Geometric mean concentrations (GMCs) of anti-tetanus antibody levels on Month 1.

	Meningococcal ACWY vaccination: • Proportion of participants achieving ≥1:4 hSBA (in participants with undetectable pre-vaccination assay titers) at Month 1 post-vaccination for serogroup C. • Geometric mean titers (GMTs) of antibodies for serogroup C at baseline and on Month 1.
Evaluate safety of tetanus and meningococcal ACWY vaccinations in AA participants treated with PF-06651600.	• Incidence of SAEs and AEs. • Incidence of SAEs and AEs leading to discontinuation.

2.2. Study Design

This is a sub-study evaluating immunogenicity to vaccine antigens following Tdap and meningococcal ACWY vaccinations in adult participants with AA enrolled in the main B7981032 study.

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

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

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

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

Table 3. Vaccine Sub-Study Additional Procedures

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

Procedure	Sub-Study Baseline (Day 1)	Sub-Study Month 1 (Day 31)	Notes Baseline visit must occur at a scheduled study visit in the main B7981032 study.
Visit	1	2	
Window	None	+5 days	

Abbreviations: ACWY = groups A, C, W-135 and Y, Tdap = tetanus and diphtheria toxoids and acellular pertussis
a. Pre-vaccination blood samples for titers will be collected based on the vaccine(s) to be administered to the participant on Day 1.
b. Participants may receive both vaccines, only Tdap vaccine, or only meningococcal ACWY vaccine.
c. Post-vaccination blood samples for titers will be collected based on the vaccine(s) received by the participant on Day 1.

Study Treatments

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

Sample Size Determination

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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoint is:

- Proportion of participants achieving a booster response from Tdap vaccination defined as 1) ≥4-fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the pre-vaccination concentration was ≤2.7 IU/mL; 2) ≥2-fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the pre-vaccination concentration was >2.7 IU/mL;

3.2. Secondary Endpoints

3.2.1. Tdap

Secondary endpoints to evaluate immune response to Tdap vaccination are:

- Proportion of participants with anti-tetanus antibody level ≥1.0 IU/mL on Month 1;
- Proportion of participants with anti-tetanus antibody level ≥0.1 IU/mL on Month 1;
- Proportion of participants with ≥4x increase in anti-tetanus antibody level from baseline;
- Fold increase in anti-tetanus levels above baseline values at Month 1;
- Geometric mean concentrations (GMCs) of anti-tetanus antibody levels on Month 1.

3.2.2. ACWY

The secondary endpoints to evaluate immune responses to meningococcal ACWY vaccination are:

- Proportion of participants achieving ≥1:8 human serum bactericidal activity (hSBA) due to ACWY vaccination (in participants with undetectable pre-vaccination assay titers) at Month 1 post-vaccination for serogroup C;
- Proportion of participants achieving ≥1:4 hSBA (in participants with undetectable pre-vaccination assay titers) at Month 1 post-vaccination for serogroup C;
- Geometric mean titers (GMTs) of antibodies for serogroup C at baseline and on Month 1.

3.3. PK Endpoints

There will be no PK endpoints defined in this sub-study.

3.4. Baseline Variables

Baseline values will be defined as the latest non-missing pre-vaccination values of the vaccine Sub-Study.

3.5. Safety Endpoints

The safety endpoints are:

- Incidence of SAEs;
- Incidence of AEs;
- Incidence of AEs leading to discontinuation.

3.5.1. Adverse Events

Only adverse events (AE) that occur during the defined risk period will be summarized in this sub-study. The risk period is defined as the period from the date of vaccination until the earliest of the following dates:

- the date of VSS Month 1 visit (if not missing) or
- the last date collected in the disposition CRF of VSS, or
- the date of VSS Day 36

3.5.2. Laboratory Data

Laboratory assessments are hematology and serum chemistry tests collected on Day 1 and Month 1 of the vaccine sub-study. On Day 1 visit, these will be collected as a part of laboratory assessments scheduled for the corresponding visit of the main study.

3.5.3. Vital Signs

Vital sign measurements are pulse rate and blood pressure collected on Day 1 and Month 1 of the vaccine sub-study. On Day 1 visit, these will be collected as a part of vital sign assessments scheduled for the corresponding visit of the main study.

3.5.4. Physical Examinations

Complete or targeted physical exams will be conducted on Day 1 according to the schedule in the main trial and targeted exams will be conducted on Month 1.

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 should include skin, heart, lung, and abdomen, neurologic function, and examination of body systems where there are symptom complaints by the participant.

4. ANALYSIS SETS

4.1. Safety Analysis Set

The Safety Analysis Set (SAS) is defined as all participants from this sub-study who receive at least 1 vaccine (Tdap or meningococcal ACWY).

4.2. Full Analysis Set

There will be two Full Analysis Sets (FAS) based on the vaccine(s) received.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

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

5.1. Hypotheses and Decision Rules

B7981032 is an open-label study hence no statistical hypotheses will be tested.

5.2. General Methods

All analyses will be descriptive in nature; there will be no formal hypothesis testing although 95% two-sided CIs will be generated.

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

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

Antibody titers or concentrations below LLOQ (or LLQ) will be set to 0.5 × LLOQ for the calculation of geometric means of GMT, GMC and fold increase in anti-tetanus antibody levels. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ. When calculating a fold increase, the assay results will be converted to 0.5 × LLOQ if assay results are < LLOQ, except when the pre-vaccination assay result is < LLOQ while the post-vaccination result is ≥ LLOQ, in which case the pre-vaccination value will be set to LLOQ.

In general, descriptive summary statistics such as number, percentage and 95% confidence interval will be presented for binary variables. Number, mean, standard deviation (sd), median, minimum, and maximum will be presented for continuous variables.

All summaries will be presented for all participants, without separating de novo participants from those orginating from Study B7931005 or B7981015.

5.3. Methods to Manage Missing Data

Data will be summarized based on observed data. Missing data will not be imputed.

If there are values recorded as “Not Done (ND)” or “Indeterminate (IND)”, they will be treated as missing values.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

- Summary: Proportion of participants with tetanus booster response.

- Population: FAS-Tdap.

- Statistical Method: number and percentage of participants with a booster response and 95% two-sided CIs based on Clopper-Pearson exact method. Booster response to tetanus vaccination is defined as:

  1) ≥4 fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the pre-vaccination concentration was ≤2.7 IU/mL;

  2) ≥2 fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the pre-vaccination concentration was >2.7 IU/mL.

6.2. Secondary Endpoints

6.2.1. Tdap

6.2.1.1. Anti-Tetanus Antibodies 1.0

- Summary: Proportion of participants with anti-tetanus antibody level ≥1.0 IU/mL on Month 1.

- Population: FAS-Tdap.

- Statistical Method: number and percentage of participants with the response and 95% two-sided CIs based on Clopper-Pearson exact method.

6.2.1.2. Anti-Tetanus Antibodies 0.1

- Summary: Proportion of participants with anti-tetanus antibody level ≥0.1 IU/mL on Month 1.

- Population: FAS-Tdap.

- Statistical Method: number and percentage of participants with the response and 95% two-sided CIs based on Clopper-Pearson exact method.

6.2.1.3. Anti-Tetanus Antibodies 4x

- Summary: Proportion of participants with ≥4x increase in anti-tetanus antibody level from baseline.

- Population: FAS-Tdap

- Statistical Method: number and percentage of participants with the response and 95% two-sided CIs based on Clopper-Pearson exact method.

6.2.1.4. Anti-Tetanus Antibodies Levels Fold Increase

- Summary: Geometric mean fold increase (GMFI) in anti-tetanus levels above baseline values at Month 1.

- Population: FAS-Tdap.
- Statistical Method: geometric mean and 95% CI based on back transformation of the natural log-transformed data.

6.2.1.5. GMC of Anti-Tetanus Antibodies

- Summary: GMCs of anti-tetanus antibody levels on Month 1.
- Population: FAS-Tdap.
- Statistical Method: geometric mean and 95% CI based on back transformation of the natural log-transformed data.

6.2.2. ACWY

6.2.2.1. hSBA Response of ≥1:8 hSBA to ACWY vaccine

- Summary: Proportion of participants with meningococcal ACWY response.
- Population: FAS-ACWY, among participants with undetectable pre-vaccination assay titers where the titers < LOD.
- Statistical Method: number and percentage of participants with the response and 95% two-sided CIs based on Clopper-Pearson exact method. Response to ACWY vaccination is defined as hSBA titer ≥1:8 at Month 1 post-vaccination for serogroup C.

6.2.2.2. hSBA Response of ≥1:4 hSBA to ACWY vaccine

- Summary: Proportion of participants with hSBA titer ≥1:4 (in participants with undetectable pre-vaccination assay titers) at Month 1 post-vaccination for serogroup C.
- Population: FAS-ACWY, among participants with undetectable pre-vaccination assay titers where the titers < LOD.
- Statistical Method: number and percentage of participants with the response and 95% two-sided CIs based on Clopper-Pearson exact method.

6.2.2.3. GMT of Antibodies for Serogroup C

- Summary: GMTs of antibodies for serogroup C at baseline and on Month 1.
- Population: FAS-ACWY.
- Statistical Method: geometric mean and 95% CI based on back transformation of the natural log-transformed data.

6.3. Safety Summaries and Analyses

Safety analysis will be based on SAS. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with CDISC and Pfizer Standards (CaPS).

6.3.1. Adverse Events

- Summary: Incidence of AEs, SAEs and AEs leading to discontinuation per the following categories:
    - AEs occurring during the risk period among participants who received the Tdap vaccination (with or without the meningococcal ACWY vaccination).
    - AEs occurring during the risk period among participants who received the meningococcal ACWY vaccination (with or without the Tdap vaccination).
    - AEs occurring during the risk period among all participants in the SAS.
- Population: SAS.
- Statistical Method: number and percentage of participants with the events reported in the same way as the main B7981032 study.

6.3.2. Laboratory Data

Laboratory data will be summarized and listed in accordance with the Pfizer reporting standards. Summaries of incidence of abnormalities will be reported.

6.3.3. Vital Signs

Vital signs will be summarized at baseline and all available post-baseline visits, in accordance with the Pfizer reporting standards.

6.3.4. Physical Examinations

Physical examinations will be summarized at baseline and all available post-baseline visits, in accordance with the Pfizer reporting standards.

6.4. Subset Analyses

No subgroup analyses will be performed.

6.5. Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics and medical history will be summarized for all participants in the sub-study. Baseline disease characteristics may also be summarized.

6.5.2. Study Conduct and Participant Disposition

Participants evaluation, disposition and discontinuation will be summarized for all participants in this sub-study.

6.5.3. Study Treatment Exposure

Study treatment exposure will be summarized as the number of participants receiving each vaccine.

6.5.4. Concomitant Medications and Nondrug Treatments

Prior drug and non-drug treatments, concomitant drug and non-drug treatments will be summarized for all participants in this sub-study.

7. INTERIM ANALYSES

There will be no interim analyses for this sub-study.

8. APPENDICES

Appendix 1. Definition and Use of Visit Windows in Reporting

Visit Label	Target Day	Analysis Visit Window
Baseline	1	Up to Sub-Study Day 1
Month 1	31	Sub-Study Day 2 to End of Sub-Study

If more than one observation falls within a visit window, the observation that is the closest to the target day will be used for the summary tables. If two visits are equally distant from the target day, the data from the later visit will be used.

Appendix 2. List of Abbreviations

Abbreviation	Term
AA	Alopecia Areata
ACWY	groups A, C, W-135 and Y
AE	Adverse Event
CaPS	Cdisc and Pfizer Standards
CI	Confidence Interval
CRF	Case Report Form
EU	European Union
FAS	Full Analysis Set
GMC	Geometric Mean Concentration
GMFI	Geometric Mean Fold Increase
GMT	Geometric Mean Titer
hSBA	Human Serum Bactericidal Activity
IgG	Immunoglobulin G antibody
IND	Indeterminate
IU/mL	International Units Per Milliliter
LOD	Limit of Detection
LLOQ/LLQ	Lower Limit of Quantification
N/A	Not Applicable
ND	Not Done
PK	Pharmacokinetic(s)
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
VHP	Voluntary Harmonisation Procedure
VSS	Vaccine Sub-Study