Protocol B1971060

A PHASE 4, OPEN-LABEL, SINGLE-ARM TRIAL TO DESCRIBE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF TRUMENBA® WHEN ADMINISTERED TO IMMUNOCOMPROMISED PARTICIPANTS ≥10 YEARS OF AGE

Statistical Analysis Plan (SAP)

Version: 1

Date: 07 Sep 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 07 Sep 2021	Original 22 Jan 2021	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B1971060. A brief description of the study design and the study objectives are given. Subsequent sections include analysis populations and the definitions of the immunogenicity and safety endpoints followed by details around statistical analysis and reporting. A list of tables, listings, and figures, mock-up tables, listings, and figures, and programming rules are prepared separately based on the methods described in this document. 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. Table 2 shows the study design.

Table 2. Study Design

	Vaccination 1	**Safety Follow-up Visit 1**	**Vaccination 2**	**Post–Vaccination 2 Blood Draw**	**Telephone Contact**
Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Approximate month	0	1	6	7	12
Vaccination	Trumenba		Trumenba		
Blood draw	20 mL			20 mL	

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary and exploratory objective are described in Table 3. The estimands to evaluate the immunogenicity objectives are based on evaluable populations (see Section 4 for definition). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Additional analyses are specified as well, including participants regardless of whether or not the participants followed the study schedules.

Table 3. List of Primary and Exploratory Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Prima1·y Immunogenicity:**	**Primary Immunogenicity:**
• To describe the immune response induced by 2 doses ofTmmenba in immunocompromised participants and historical age- and sex-matched healthy participants as measured by hSBA perfo1med with 4 prima1y MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein.	In immunocompromised participants or historical age- and sex-matched healthy participants who are sepru·ately receiving 2 doses of study intervention and are in compliance with key protocol criteria (evaluable participants): • The propo1tion of participants with hSBA titer 2:: LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each of the 4 primary MnB test strains 1 month after Vaccination 2.	• hSBA titer for each of the primruy MenB test strains (A22, A56, B24, and B44).
Primary Safety:	**P1·imary Safety:**	**Prima1·y Safety:**
• To evaluate the safety profile ofTmmenba in immunocompromised participants and historical age- and sex-matched healthy participants.	In immunocompromised participants or historical age- and sex-matched healthy participants separately, who ru·e receiving at least **1** dose of study intervention: 1. The percentage of pa1ticipants repo1ting local reactions, systemic events, and use of antipyretic medication within 7 days after each vaccination with Tl1llllenba. 2. The percentage of pa1ticipants with at least **1** SAE and at least 1 MAE during the following time periods: • 30 Days after each vaccination. • 30 Days after any vaccination. • During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2). • During the follow-up phase (from **1** month after Vaccination 2 through 6 months after Vaccination 2). • From Vaccination **1** through 6 months after Vaccination 2. 3. The percentages of participants with at least **1** AE occun-ing during the following time periods: • 30 Days after each vaccination. • 30 Days after any vaccination. • During the vaccination phase (from Vaccination 1 through **1** month after Vaccination 2).	• Local reactions (pain at the injection site, redness, and swelling). • Systemic events (fever, vomiting, dian-hea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain). • Use of antipyretic medication. • AEs. • SAEs. • MAEs. • Immediate AEs. • NDCMCs. • Days missing from school or work because of AEs.

Table 3. List of Primary and Exploratory Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
	4. The percentage of pa1ticipants with at least **1** immediate AE after each vaccination. 5. The percentage of pa1ticipants with at least **1** NDCMC occun-ing during the following time periods: • Dm-ing the vaccination phase (from Vaccination 1 through **1** month after Vaccination 2). • Dm-ing the follow-up phase (from **1** month after Vaccination 2 through 6 months after Vaccination 2). • From Vaccination **1** through 6 months after Vaccination 2. 6. Number of days pa1ticipants missed school or work because of AEs dm-ing the vaccination phase (from Vaccination 1 throuoh **1** month after Vaccination 2 .	
Exploratory hnmunogenicity:	**Exploratory Immunogenicity:**	**Exploratory Immunogenicity:**
[redacted] CCI	[redacted]	[redacted]

2.2. Study Design

This is a Phase 4, open-label, single-aim, multicenter trial in which up to 50 immunocompromised paiticipants10 yeai·s of age with asplenia (anatomic or functional) or complement deficiency will be emolled and receive Tmmenba®on a 2-dose, 0- and 6-month schedule. All pa1ticipants will be naive to any meningococcal serogroup B vaccine prior to emollment.

Historical data from age- and sex-matched healthy paiticipants from a pivotal Phase 3 MnB study (that has previously completed the primaiy analysis) will be used as a reference for the safety and immunogenicity ofTnnnenba. Healthy adolescents and young adults (10 to <26 yeai·s of age) from Study B1971057 will be randomly selected as controls (Section 2.2.1).

For this study, immunocompromised participants are individuals at increased risk for meningococcal disease due to anatomic asplenia or functional asplenia (eg, sickle cell anemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor H, or factor D).

Enrolled participants will be vaccinated with 2 doses of Trumenba at Months 0 and 6 (Visits 1 and 3). Blood samples (approximately 20 mL per visit) for immunogenicity analysis by hSBA (performed with 4 primary MenB test strains as detailed in Section 3) will be collected prior to Vaccination 1 and 1 month after Vaccination 2 (Visits 1 and 4). Given the immunocompromised population enrolled in this study, participants will receive an on-site follow-up visit 1 month after Vaccination 1 (Visit 2). Participants will attend 4 study visits, and a telephone contact will be made at Visit 5 (6 months after the last vaccination).

2.2.1. Historical Age- and Sex-Matched Healthy Controls

Healthy adolescents and young adults (10 to <26 years of age) from Study B1971057 (Stage 1) will be randomly selected and a historical age- and sex-matched healthy control group will be used to provide context and assist with the interpretation of the immunogenicity and safety data for the immunocompromised participants. The safety and immunogenicity data will be reported separately for the immunocompromised and age- and sex-matched healthy control participants. Study B1971057 is a pivotal Phase 3, randomized, observer-blinded multicenter trial for which the primary analysis has been completed. In Study B1971057, Group 2 and 4 (Stage 1) participants received vaccinations with Trumenba at Visit 1 (Month 0) and Visit 3 (Month 6). Blood samples (for testing primary MenB test strains for primary and secondary immunogenicity endpoints in Trumenba groups) were collected at Visit 1 (before Vaccination 1) and Visit 4 (1 month after Vaccination 2). Safety telephone contact was scheduled at Visit 5 (6 months after Vaccination 2) for safety endpoints. Refer to the Study B1971057 SAP for detailed information on the visit schedule, endpoints, methods, and planned analyses.

Study B1971057 followed the same 0- and 6-month dosing schedule and used the same methodology for assessment of immunogenicity and safety as are planned for Study B1971060. Therefore, because of the similarity of study designs between the 2 studies, healthy adolescents and young adults (10 to <26 years of age at first vaccination) who were enrolled in B1971057 and who were randomized to Group 2 or 4 will be selected as the control group for immunocompromised participants.

The selection of healthy controls will be performed following the database release for Study B1971060 when the final immunogenicity analysis populations have been defined. For immunocompromised participants 10 to <26 years of age in this study, age- and sex-matched healthy control participants will be randomly selected from Study B1971057 (Trumenba groups only). For immunocompromised participants older than 25 years of age in this study, the age- and sex-matched heathy controls will be randomly selected from participants of the same sex at 25 years of age from Study B1971057. A participant in the evaluable population in B1971060 will be matched with a participants in the evaluable population from B1971057.

For participants who are not in the evaluable population in B1971060 but who are in the mITT population, age- and sex-matched healthy participants will be randomly selected from B1971057 participants who are not in the evaluable population but are in the mITT population and have recieved the same number of doses. For any B1971060 participant who is not included in the mITT population but is randomized, a corresponding age- and sex-matched participant from B1971057 (Trumenba groups) who is not in the mITT population will be randomly selected. For all scenarios with age- and sex-matched controls: the matching is done based on participants with the same sex where the matched healthy control may be up to 2 years younger or older than the participant in B1971060.

Healthy participants will be randomly selected as controls once.

The analysis data sets from Study B1971057 Stage 1 will be used for selection of age- and sex-matched healthy controls from participants randomized to Trumenba in Study B1971057 (Stage 1).

The immunogenicity and safety will be reported in the historical age- and sex-matched controls for the endpoints, time points and analysis intervals, and analysis populations corresponding to those for the immunocompromised participants.

2.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the Study Assessments and Procedures section of the protocol for detailed info1mation on each procedure and assessment required for compliance with the protocol.

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

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Visit Description	**Vaccination 1**	**Safety Follow-up Visit**	**Vaccination 2**	**Post-Vaccination 2 Blood Draw**	**Telephone Contact**
Approximate Month	0	**1**	**6**	7	**6 Months After Last Study Vaccination**
Visit Window	**Dayl**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days Afte1· Visit 3**
Infonued consent	X				
Review eligibility criteria	X				
Demography	X				
Confinu continued eligibility"		X	X	X	
Medical history and physical examination	X				
Record previous pneumococcal and meningococcal sero1Zrouo ACWY vaccinations	X				
Record blood transfusions within prior 3 months	X				
Urine pregnancy test for all female participants	X		X		
Obtain prevaccination oral temperature	X		X		
IVRS/IWRS kit assignment	X		X		
Obtain blood sample	20mL			20mL	
Study intervention administration and observationb	X		X		
Record nonstudy vaccinations and any blood transfusions		X	X	X	
Provide the participant with a contact card	X				
Provide the participant with a memo,y aid		X		X	

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Visit Description	**Vaccination 1**	**Safety Follow-up Visit**	**Vaccination 2**	**Post-Vaccination 2 Blood Draw**	**Telephone Contact**
Approximate Month	0	**1**	**6**	7	**6 Months After Last Study Vaccination**
Visit Window	**Dayl**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days Afte1· Visit 3**
Provide the pa1ticipant with e-dia1y or ensure dia1y app downloaded	X		X		
Review and collect e-diary		X		X	
Provide caliper, measuring tape, and the1mometer, if necessary	X		X		
Assess reactogenicity and record use of antipyretic medicationc	Daylto7		Day 1 to 7		
Collect e-dia1y, if applicable		X		X	
Complete Study Visit/Telephone Contact AE Checklistd		X	X	X	X
Record concomitant medications used to treat AEs	X	X	X	X	X
(S)AE collection appropriate for the visif	X	X	X	X	X

Abbreviations: ACWY = *Neisseria meningitidis* serogroups A, C, W-135, and Y; e ia1y = electronic diary; IVRS = interactive voice response system; IWRS = interactive Weh-based response system.

a. Ensure that the participant continues to be eligible for the study, does not meet any tempora1y delay criteria, and continues to comply with contraception requirements, as appropriate.
b. Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions.
c. Between visits, review the e-dia1y data online at frequent intervals. Contact the pa1ticipant/parent(s)/legal guardian in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the e-dia1y was completed.
d. Checklist includes questions regarding newly diagnosed chronic medical conditions; hospitalizations, visits to other medical facilities, medication use, and missed days of school or work due to AEs; and neuroinflamm.atoryand autoimmune conditions, such as transverse myelitis, uveitis, optic netu-itis, and multiple sclerosis.
e. A follow-up contact with the pa1ticipant must be scheduled at the end of the AE/SAE active collection period as defined in Section 8.3.1 of the protocol.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

The primary immunogenicity, safety, and exploratory immunogenicity endpoints are applicable to both immunocompromised participants in Study B1971060 and age- and sex-matched healthy controls (10 to <26 years of age) who were randomized to Group 2 or 4 (Trumenba groups) in Study B1971057.

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

- hSBA titers for each of the primary MenB test strains (A22, A56, B24, and B44) ≥ LLOQ 1 month after Vaccination 2.

Validated hSBA LODs and LLOQs for the 4 primary MenB strains are defined as shown in Table 4.

Table 4. Validated hSBA LODs and LLOQs for the 4 Primary MnB Strains

Strain LP2086 Variant	LOD	LLOQ
A22	1:4	1:16
A56	1:4	1:8
B24	1:4	1:8
B44	1:4	1:8

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; LP2086 = lipoprotein 2086; MnB = *Neisseria meningitidis* serogroup B.

At each visit where assay titers are available (Visit 1 and Visit 4), participants with MenB test strain (A22, A56, B24, and B44) hSBA titers ≥ LLOQ will be derived as follows:

= •, if the assay result is missing, indeterminate, or otherwise unavailable;

= 1, if the assay result meets the specific LLOQ value;

= 0, if the assay result does not meet the specific LLOQ value.

3.1.2. Primary Safety Endpoints

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after each vaccination and after any vaccination.
- Systemic events (fever, vomiting, diaIThea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain) within 7 days after each vaccination and after any vaccination.
- Use of antipyretic medications within 7 days after each vaccination and after any vaccination.
- AEs within 30 days after each vaccination and after any vaccination, and during the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
- SAEs and MAEs within 30 days after each vaccination and after any vaccination, during the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2), during the follow-up phase (from 1 month after Vaccination 2 through 6 months after Vaccination 2), and from Vaccination 1 through 6 months after Vaccination 2.
- Immediate AEs after each vaccination.
- NDCMCs during the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2), the follow-up phase (from 1 month after Vaccination 2 through 6 months after Vaccination 2), and from Vaccination 1 through 6 months after Vaccination 2.
- Days missing from school or work because of AEs during the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).

3.2. Secondary Endpoints

Not applicable.

3.3. Exploratory Endpoints

CCI [redacted]

[redacted]

I [redacted]

I [redacted].

[redacted]

3.4. Baseline Variables

3.4.1. Demographic, Medical History, and Baseline Characteristic Variables

Demographic variables collected at Visit 1 include sex (male or female), race, ethnicity, and date of bi1ih. Race collected includes:

- Black or African American
- American Indian or Alaskan native
- Asian
- Native Hawaiian or other Pacific Islander
- White
- Not repo1ied

Ethnicity collected includes:

- Hispanic or Latino
- Non-Hispanic/non-Latino
- Not repo1ied

Age at each vaccination (in days) will be derived as (vaccination date - date of bi1ih + 1). For paiiicipants who were emolled but not vaccinated, the consent date will be used in place of the date of Vaccination 1 for the calculation of the age at first vaccination.

In cases where more than 1 catego1y is selected for race, the paiiicipant will be counted under the catego1y "multiracial" for analysis.

Medical histo1y will be assessed at Visit 1 and categorized according to the cmTent version (at the time of repo1iing) ofMedDRA.

Physical examination will be assessed prior to vaccination at Visit 1 and each body system examined will be recorded in the CRF as normal, abnormal, or not done.

3.4.2. E-Diary Completion

For any given day, an e-diary will be transmitted and considered complete if all expected data (the 3 local reactions, the 8 systemic events including fever, and the use of antipyretic medications) are available. If all data are missing for all items on the e-diary, for all days following vaccination, the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

The following e-diary compliance variables will be provided for each vaccination:

- Compliance per day: the numerator is the number of participants who completed (transmitted) the e-diary on a given day (Day 1 to Day 7, where Day 1 is the day of each vaccination) and the denominator is the total number of participants who received the vaccination.

- At least X days: the numerator is the number of participants who completed (transmitted) the e-diary on X days and the denominator is the total number of participants who received a vaccination (X = 1 through 7; compliance will be computed for each value of X).

- All 7 days: the numerator is the number of participants who completed (transmitted) the e-diary on all 7 days and the denominator is the total number of participants who received a vaccination.

3.4.3. Nonstudy Vaccines and Concomitant Medications

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD through Visit 4 will be recorded on the CRF.

The name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat an AE (excluding events recorded only in the e-diary) from the signing of the ICD through Visit 5 will be recorded on the CRF.

The date and type of any blood transfusion (eg, whole blood, packed cells) received within the 3 months before enrollment through Visit 4 will be recorded on the CRF.

Nonstudy vaccines and concomitant medications permitted during the study include:

- All treatments that reflect standard of care for immunocompromised participants are permitted.

- Blood transfusions are permitted during the study.

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. In such situations, effort should be made to appropriately plan the administration of study intervention around dosing of the pandemic vaccine.

- Nonstudy vaccines that are part of recommended immunization schedules are allowed at any time during the study but should not be administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) of study intervention administration.

- Antipyretics and other pain medications to treat symptoms associated with study intervention are permitted.

- Local anesthetic may be applied before blood draw.

- Topical antibiotics are permitted.

- Topical and inhaled corticosteroids are permitted.

Treatments will be categorized according to the current version (at the time of reporting) of the WHO Drug Dictionary.

3.5. Safety Endpoints

3.5.1. Local Reactions

Local reaction data are solicited AEs. The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site of study intervention, from Day 1 through Day 7 after each vaccination, where Day 1 is the day of vaccination. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence

For each local reaction, the derivation of whether or not the specific reaction occurred on each day and "any day (Days 1-7, where Day 1 is the day of vaccination)" will be made. The variable will be calculated for each vaccination as well as overall reactions for any vaccination. The derivation of this variable is given in Table 5.

Table 5. Derived Variables for Local Reactions

Variable	Yes (1)[a]	No (0)[b]	Missing (.)
Each day (Days 1-7)	Participant/parent/legal guardian reports the reaction as "mild," "moderate," or "severe" on each individual day.	Participant/parent/legal guardian reports the reaction as "none" on the individual day.	Participant did not report on the reaction on the individual day.

Table 5. Derived Variables for Local Reactions

Variable	Yes (1)[a]	No (0)[b]	Missing (.)
Any day (Days 1-7)	Participant/parent/legal guardian reports the reaction as "mild," "moderate," or "severe" on any day (Days 1-7).	Participant/parent legal guardian reports the reaction as "none" on all 7 days or as a combination of "none" and missing on all 7 days.	Participant did not report on the reaction on any of the 7 days.

a. For redness and swelling, "mild," "moderate, and "severe" categories are based on the caliper size reported from the e-diary and defined in Table 6.
b. For redness and swelling, "none" means 0 to 4 caliper units reported in the e-diary.

Severity and Maximum Severity

A caliper (measuring device) is used to measure the redness or swelling of the injection site area. Caliper units (range: 1-21+) are converted to centimeters according to 1 caliper unit = 0.5 centimeters and then categorized as none, mild, moderate, or severe based on the grading scale of local reactions in Table 6. The caliper will be used to measure and to report the largest diameter of a redness or swelling at the injection site. In the event that a caliper measurement is between 2 values, the higher value should be reported. Pain at the injection site will be assessed by the participant/parent(s)/legal guardian(s) according to the grading scale in Table 7. The measurements will then be recorded in the e-diary.

Table 6. Grading of Redness and Swelling

None	0 to 2.0 cm (0 to 4 caliper units)
Mild	>2.0 to 5.0 cm (5 to 10 caliper units)
Moderate	>5.0 to 10.0 cm (11 to 20 caliper units)
Severe	>10.0 cm (>20 caliper units)

Table 7. Grading of Pain at Injection Site

Mild	Does not interfere with activity
Moderate	Interferes with activity
Severe	Prevents daily activity

The maximum severity (highest grading) of each local reaction within 7 days after vaccination will be derived for each vaccination as well as for any vaccination. The maximum severity will be derived as follows:

= •, if values are missing for all days (Days 1 to 7);

= 0, if the participant's parent(s)/legal guardian(s) reports all reactions as "none" or a combination of missing and "none" for all days (Days 1 to 7);

= *highest grade* (maximum severity) within 7 days after vaccination, if the answer is not "none" for at least 1 day.

Duration

For participants experiencing any local reactions (or those with derived reaction presence in Table 5), the maximum duration (last day of reaction - first day of reaction + 1) will be derived for the study vaccination. Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the participant diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing.

For reactions that continue into the next vaccination visit, the duration will be calculated in a segmented fashion. The reaction end date will be set to the day prior to the next vaccination and will have a new start date as the day of next vaccination. The duration will be calculated separately from the new start date to the date of resolution. Participants with reactions spanning multiple vaccination visits will be included in a footnote.

Participants with no reported reaction have no data for duration.

Onset Day

The onset day of each local reaction will be derived. The onset day is defined as the first day of reporting the reaction with any severity after vaccination.

In summary, the following variables will be derived for local reactions:

- Each local reaction on each day (Days 1 to 7) after each vaccination.
- Each local reaction on any day (Days 1 to 7) after each vaccination and any vaccination.
- Any local reaction on any day (Days 1 to 7) after each vaccination and after any vaccination.
- Maximum severity of each local reaction on any day (Days 1 to 7) after each vaccination and after any vaccination.

- Maximum duration of each local reaction after each vaccination.
- Onset day of each local reaction after each vaccination.

3.5.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain, from Day 1 through Day 7, where Day 1 is the day of vaccination. The systemic events will be assessed by participants or parents/legal guardians as mild, moderate, or severe according to the grading scale in Table 8.

Table 8. Grading of Systemic Events Other Than Fever

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires IV hydration
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Muscle pain (other than muscle pain at the injection site)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity

Abbreviation: IV = intravenous.

Maximum oral temperature range over the period from Day 1 through Day 7 after each vaccination will be mapped into the ranges described in Table 9 for summary of maximum temperature. The highest temperature for each day will be recorded in the e-diary. Fever is defined as temperature of ≥38.0°C (100.4°F).

Table 9. Severity Scale for Fever

Temperature 38.0°C to 38.4°C (100.4°F to 101.1°F)
Temperature >38.4°C to 38.9°C (101.2°F to 102.0°F)
Temperature >38.9°C to 40.0°C (102.1°F to 104.0°F)
Temperature >40.0°C (>104.0°F)

For each systemic event, the following variables will be available, similar to local reactions:

1. Each systemic event on each day (Days 1 to 7) after each vaccination.
2. Each systemic event on any day (Days 1 to 7) after each vaccination and after any vaccination.
3. Any systemic event on any day (Days 1 to 7) after each vaccination and after any vaccination.
4. Maximum severity of each systemic event on any day (Days 1 to 7) after each vaccination and after any vaccination.
5. Maximum duration of each systemic event after each vaccination.
6. Onset day of each local reaction after each vaccination.

The derivation of severity, maximum severity, duration, and onset day for systemic events is similar to the derivation of the variables for local reactions (Section 3.5.1).

3.5.3. Use of Antipyretic Medication

The use of antipyretic medication (yes/no) will be recorded in the e-diary for 7 days (Day 1 to Day 7) after each vaccination.

The following variables will be derived:

1. Use of antipyretic medication on each day (Days 1 to 7) after each vaccination.
2. Use of antipyretic medication on any day (Days 1 to 7) after each vaccination and after any vaccination.
3. Maximum duration of use of antipyretic medication after each vaccination.

Three analysis intervals will be applied to reactogenicity data (Table 10).

Table 10. Analysis Intervals for Reactogenicity Data

No.	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)
1	Vaccination 1	Vaccination 1 safety	Vax 1 date	Vax 1 date + 6 days (or until date of resolution)
2	Vaccination 2	Vaccination 2 safety	Vax 2 date	Vax 2 date + 6 days (or until date of resolution)
3	Any vaccination	Safety	Vax 1 or Vax 2 date	Vax 1 or Vax 2 date + 6 days (or until date of resolution)

3.5.4. Adverse Events

The relationship between (S)AEs and the study intervention will be characterized as related or not related as determined by investigators and as described in the protocol. The severity of AEs will be characterized as mild, moderate, and severe. Immediate AEs will be assessed within the first 30 minutes after each vaccination.

An NDCMC is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility, and participants who missed days of school or work because of an AE will be captured via the AE checklist (Section 2.3).

(S)AEs will be actively collected for each participant beginning from the time the participant or parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 4. At Month 12 (Visit 5, telephone contact), the parent(s)/legal guardian or participant will be contacted by telephone to inquire about AEs, SAEs, MAEs, NDCMCs, and days missing from school or work because of AEs that resulted in evaluation at a medical facility since Visit 4.

Significant medical occurrences that begin before consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. All events collected on the CRF will be categorized according to the current version of MedDRA (at the time of reporting).

There will be 6 analysis intervals for the AE data collected via the CRF (Table 11). The analysis populations used for these intervals are described in detail in Section 4.

Table 11. Analysis Intervals for AEs, SAEs, MAEs, NDCMCs, and Days Missing School or Work Because of AEs

No.	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
1	Within 30 days after Vaccination 1	Vaccination 1 safety	Vax 1 date	Vax 1 date + 30 days	AEs, SAEs, MAEs
2	Within 30 days after Vaccination 2	Vaccination 2 safety	Vax 2 date	Vax 2 date + 30 days	AEs, SAEs, MAEs
3	Within 30 days after any vaccination	Safety	Vax 1 date or Vax 2 date	Vax 1 date + 30 days or Vax 2 date + 30 days	AEs, SAEs, MAEs
4	During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2)	Safety	Visit 1 date	Visit 4 date	AEs, SAEs, MAEs, NDCMCs, days missing from school or work because of AEs

Table 11. Analysis Intervals for AEs, SAEs, MAEs, NDCMCs, and Days Missing School or Work Because of AEs

No.	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
5	During the follow-up phase (from 1 month after Vaccination 2 through 6 months after Vaccination 2)	Follow-up safety	Visit 4 date + 1	Visit 5 date	SAEs, MAEs, NDCMCs
6	From Vaccination 1 through 6 months after Vaccination 2	Safety	Visit 1 date	Visit 5 date	SAEs, MAEs, NDCMCs

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.

Two analysis intervals will be applied to immediate AEs (Table 12).

Table 12. Analysis Intervals for Immediate AEs

No.	Analysis Interval	Analysis Population	Interval Start Date/Time (Inclusive)	Interval Stop Date/Time (Inclusive)
1	Dose 1	Vaccination 1 safety	Vax 1 time	Vax 1 time + 30 minutes
2	Dose 2	Vaccination 2 safety	Vax 2 time	Vax 2 time + 30 minutes

3.5.5. Pregnancy Testing

A pregnancy test for all female participants will be conducted at Visits 1 and 3.

3.5.6. Laboratory Data

Laboratory assessments will not be collected for this study.

3.5.7. Medical Device Errors

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used. If a medical device error involves an AE, it will be summarized according to AE reporting conventions.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

The analysis populations for immunocompromised participants are defined as below. The age- and sex-matched healthy controls (10 to <26 years) from historical data share the same analysis population definitions. Refer to the Study B1971057 SAP (Version 4, 17 May 2021, Section 4) for the description of analysis sets for the age- and sex-matched healthy controls. In Study B1971057, the study-intervention-allocated population was called the ITT population.

Participant Analysis Set	Description
Enrolled	All participants who sign the ICD, or whose parent(s)/legal guardian(s) sign the ICD.
Study intervention allocated	All participants who are assigned a randomization (participant identification) number in the IRT system.
Evaluable	All participants who were eligible, received all doses of the study intervention according to the vaccine schedule, had blood drawn for assay testing within the required time frames, had valid and determinate assay results for the proposed analysis, and had no major protocol deviations.
mITT	All participants who have at least 1 valid and determinate MnB assay result available at any time point from Day 1 through 1 month after the second vaccination (Visit 4 for this study).
Safety	All enrolled participants who received at least 1 dose of the study intervention and have safety data reported after vaccination.

Defined Population for Analysis	Description
Evaluable immunogenicity	All participants who 1. Were eligible through 1 month after Vaccination 2. 2. Received the study intervention at Visit 1 and Visit 3 as randomized. 3. Had blood drawn for assay testing within the required time frames at Visit 1 (before Vaccination 1) and 1 month after Vaccination 2 (28-42 days after Visit 3). 4. Had at least 1 valid and determinate assay result 1 month after Vaccination 2. 5. Received no prohibited vaccines or medications through Visit 4. 6. Had no major protocol deviations through Visit 4.
Vaccination 1 safety	All participants who received the first dose of study intervention at Visit 1 and for whom safety information is available from Visit 1 to prior to Visit 3.
Vaccination 2 safety	All participants who received the second dose of study intervention at Visit 3 and for whom safety information is available from Visit 3 up to and including Visit 4.
Follow-up safety	All participants who received at least 1 dose of study intervention and for whom safety information is available from after Visit 4 up to and including Visit 5.

For determination of the evaluable immunogenicity population(s), items 1 through 4 will be computerized checks of the data, while items 5 and 6 will be determined by clinical review. A major protocol violation is a protocol violation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The global medical monitor from the sponsor will identify those participants with a protocol violation prior to the immunogenicity analysis performed for the study.

4.1. Historical Age- and Sex-Matched Healthy Controls

The selection criteria for age- and sex-matched healthy controls from historical data are stated in Section 2.2.

4.2. Vaccine Misallocation

- Vaccinated but no randomization number assigned: These participants will be included in the safety population for safety analysis, but will be excluded from immunogenicity analyses.

- Enrolled with randomized number assigned but not vaccinated: These participants will be excluded from any safety analyses. They may be included in the mITT population if any assay results are available and will be reported under their randomized group for immunogenicity analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No specific hypotheses will be tested in this study.

5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the proportion (%) and the n (the numerator) and N (the denominator) used in the calculation of the proportion.

5.2.1. Analyses for Binary Endpoints

The number and percentage of participants in each category will be summarized. The exact 2-sided 95% CIs for percentages, and for difference in percentages, will also be presented, where appropriate. The exact 2-sided 95% CIs for the proportion will be constructed by the Clopper-Pearson method described by Agresti.[1] The exact 2-sided 95% CIs will be presented in terms of percentages.

All safety endpoints (including reactogenicity data recorded from the e-diary and AE data recorded from the CRF) will be summarized with percentages and exact 2-sided 95% CIs (Clopper-Pearson method).

5.2.2. Analyses for Continuous Endpoints

RCDCs for hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44) for the available time points may be generated.

Days in which a participant missed school and/or work will be captured on the AE checklist. The total number of missed days of school and/or work and corresponding descriptive summary statistics will be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms for handling missing AE start dates will be applied according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

If the withdrawal rate of Study B1971060 exceeds 15%, then an additional sensitivity analysis will be planned to study the percentage of participants who either withdraw from the study or have an AE. This is to be done descriptively to show the results separately for immunocompromised participants and age- and sex-matched healthy controls.

5.3.1.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 7-day e-diary data are available, the "any day (Days 1-7)" data will be considered nonmissing. Participants are excluded from the analysis if they do not receive the particular dose or the safety data are missing on all days within the interval.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing. The e-diary transmission and completion status will be summarized per Section 6.5.4. The e-diary completion summary will provide the missing data information on the reactogenicity data.

Based on the available study data from the bivalent rLP2086 development program, missing reactogenicity data are negligible, which is consistent with Li et al (2011).[2] No sensitivity analysis is planned for reactogenicity data.

5.3.2. Immunogenicity Data

As assay data are expected to be missing completely at random, the primary analysis for the primary objectives will be based upon the observed, determinate observations. No imputation will be performed. The proportion of participants with missing immunogenicity data may be summarized at each blood sampling visit for the hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44). The denominator will be the number of participants randomized. The category of missing reasons (QNS, indeterminate, not done, dropout) may also be summarized.

Both the evaluable population and the mITT population will be used for the analysis of immunogenicity results. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis. For the hSBA results, the following values will be set to missing: QNS (insufficient sera), indeterminate results, and not done. Participants without blood draw (ie, dropout) will also be considered to have missing data for immunogenicity.

6. ANALYSES AND SUMMARIES

Study objectives, endpoints, estimands, and study design are described in Section 2. Below are the planned analyses by each endpoint. Descriptive summary statistics for each analysis will be summarized separately for the immunocompromised participants, and for the age- and sex-matched healthy controls (10 to <26 years of age at first vaccination) who were enrolled in Study B1971057 and randomized to Group 2 or 4 (Trumenba groups). Section 4 includes further details about the study analysis sets used.

Missing values of e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analyses for safety endpoints.

6.1. Primary Endpoints

6.1.1. Primary Immunogenicity Endpoints

The primary immunogenicity endpoints will use the hypothetical estimand strategy, which estimates the vaccine immunogenicity in the hypothetical setting where participants follow the study schedule and protocol requirements as directed. For the analyses using the evaluable immunogenicity population, all participants with an intercurrent event (major protocol violation, discontinuation of study participation, etc) will be excluded. Major protocol violations will be determined by clinical review (see Section 4 for major protocol deviations identified and leading to exclusions from the evaluable population). For the analyses using the mITT population, those participants with major protocol violations will be included.

6.1.1.1. hSBA Titer for Primary MenB Test Strains (A22, A56, B24, and B44)

6.1.1.1.1. Main Analysis

- Summary: The percentage of participants achieving an hSBA titer (A22) ≥1:16, and hSBA titer (A56, B24, and B44) ≥1:8, at baseline and 1 month after Vaccination 2. The descriptive analysis will be displayed separately for immunocompromised participants, and for age- and sex-matched healthy controls from historical data.

- Analysis sets: The evaluable immunogenicity population for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized and according to the analysis set to which they belong as defined in Section 4.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each primary MenB test strain, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants achieving hSBA titer ≥ LLOQ from each participant group will be presented.

6.1.1.1.2. Sensitivity/Supplementary Analyses

The main analysis will also be performed on the mITT population from immunocompromised participants, and the age- and sex-matched healthy controls (defined in Section 4).

6.1.2. Primary Safety Endpoints

The primary safety endpoints will use the treatment policy strategy and estimate the safety proportion regardless of whether an intercurrent event occurs. All the safety data collected will be included and will be reported according to the vaccine received.

6.1.2.1. Local Reactions Within 7 Days After Each Vaccination

- Summary: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each vaccination (Section 2.1). The descriptive analyses will be summarized separately for immunocompromised participants, and for age- and sex-matched healthy controls from historical data.

- Analysis set: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing e-diary data will not be imputed.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each group, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI will be presented by participant group for the following variables:

  - Presence or absence of each local reaction on any day (Days 1-7) after vaccination.

  - Presence or absence of any local reaction on any day (Days 1-7) after vaccination.

  - Maximum severity of each local reaction on any day (Days 1-7) after vaccination.

6.1.2.2. Systemic Events Within 7 Days After Each Vaccination

- Summary: The percentage of participants reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain) within 7 days after each vaccination (Section 2.1). The descriptive analyses will be summarized separately for immunocompromised participants, and for age- and sex-matched healthy controls from historical data.

- Analysis set: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing e-diary data will not be imputed.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each group, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI will be presented by participant group for the following variables:

  - Presence or absence of each systemic event on any day (Days 1-7) after vaccination.

  - Presence or absence of any systemic event on any day (Days 1-7) after vaccination.

  - Maximum severity of each systemic event on any day (Days 1-7) after vaccination.

6.1.2.3. Use of Antipyretic Medications Within 7 Days After Each Vaccination

- Summary: The percentage of participants reporting use of antipyretic medication within 7 days after each vaccination (Section 2.1). The descriptive analyses will be displayed separately for immunocompromised participants, and for age- and sex-matched healthy controls from historical data.

- Analysis sets: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing e-diary data will not be imputed.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each participant group, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI will be presented for the following variable:

    - Use of antipyretic medication on any day (Days 1-7) after vaccination.

6.1.2.4. Adverse Events

- Summary: The percentages of participants with at least 1 AE occurring during the 30 days after each vaccination, during the 30 days after any vaccination, and during the vaccination phase (Section 2.1). The descriptive analyses will be presented separately for immunocompromised participants, and for age- and sex-matched healthy controls from historical data.

- Analysis sets: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs will be provided for all events.

- Reporting results: For each participant group, the numbers and percentages of participants with AEs for the analysis intervals defined in Table 11 will be summarized. The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.1.2.5. Serious Adverse Events and Medically Attended Adverse Events

- Summary: The percentages of participants with at least 1 SAE and at least 1 MAE occurring during the 30 days after each vaccination, during the 30 days after any vaccination, during the vaccination phase, during the follow-up phase, and from Vaccination 1 through 6 months after Vaccination 2 (Section 2.1). The descriptive analyses will be displayed separately for immunocompromised participants, and for age- and sex-matched healthy controls from historical data.

- Analysis sets: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each participant group, the numbers and percentages of participants with SAEs and MAEs for the analysis intervals defined in Table 10 will be summarized. The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI will be presented for any event.

6.1.2.6. Immediate Adverse Events

- Summary: The percentages of participants with at least 1 immediate AE after each vaccination (Section 2.1).

- Analysis sets: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each participant group, the numbers and percentages of participants with AEs occurring within the 30-minute observation period immediately after vaccination according to the analysis intervals defined in Table 12 will be summarized. The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI will be presented for any event.

6.1.2.7. Newly Diagnosed Chronic Medical Conditions

- Summary: The percentages of participants with at least 1 NDCMC during the vaccination phase, during the follow-up phase, and from Vaccination 1 through 6 months after Vaccination 2 (Section 2.1).

- Analysis sets: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each participant group, the numbers and percentages of participants with AEs for the analysis intervals defined in Table 10 will be summarized. The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI will be presented for any event.

6.1.2.8. Days Missing From School or Work Because of AEs

- Summary: Number of days participants missed school or work because of AEs during the vaccination phase (Section 2.1).

- Analysis sets: Safety populations for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. Refer to Section 4 for visit-specific populations.

- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Reporting results: For each participant group, the numbers of days participants missed school or work because of AEs for the analysis intervals defined in Table 10 will be summarized.

6.2. Secondary Endpoints

Not applicable.

6.3. Exploratory Endpoints

CCI

[redacted]

6.3.1.1.2. Sensitivity/Supplementary Analyses

The main analysis will also be perfo1med on the mITT population from immunocompromised pa1ticipants, and the age- and sex-matched healthy controls (defined in Section 4).

6.4. Subset Analyses

Subgroup analyses may be performed on the primary immunogenicity and safety endpoints described in Section 6.1. No subgroup analysis is planned for rare events (endpoints with less than 1% of participants in any group). Subgroups include sex and race.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic, Medical History, and Baseline Characteristics

The safety populations will be used to generate demographic tables. All summaries will be presented for the immunocompromised and age- and sex-matched healthy control participants.

Variables defined in Section 3.4.1 will be reported according to Pfizer standard summary reporting.

Medical history and baseline physical examination will be summarized descriptively.

6.5.2. Study Conduct and Participant Disposition

All immunocompromised participants enrolled in the study, and age- and sex-matched healthy controls selected from historical data, will be included in the disposition summaries. The summaries will be conducted separately for the 2 groups.

Disposition summaries include:

- N and % of participants included in each study population (mITT population, evaluable immunogenicity population).
- N and % of participants receiving each vaccination.
- N and % of participants completing all the vaccination phase visits (Visit 1 to Visit 4) and the follow-up phase visit (Visit 5).
- N and % of participants who withdrew during the study (Visits 1 to 5) and reason for withdrawal.

For each blood draw, the numbers and percentages of participants enrolled, vaccinated at each visit (Visits 1 and 3), and providing blood samples within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for the immunocompromised participants and for the historical data of the age- and sex-matched healthy participants separately.

6.5.3. Study Vaccine Exposure

Study vaccination data, temporary delays and reasons for vaccination delays, and noncompliant vaccine administration and reasons may be listed by vaccine group according to the vaccine administered. Participants not receiving vaccination may be listed.

6.5.4. E-Diary Completion

E-diary compliance as defined in Section 3.4.2 will be summarized for each vaccination (Vaccination 1, Vaccination 2) using descriptive statistics. The safety population will be used to generate the summary reports. The denominator for the e-diary compliance rates will be the total number of participants who received the specific vaccination.

6.5.5. Concomitant Medications and Nondrug Treatments

Nonstudy vaccines and concomitant medications will be categorized according to the WHO Drug Dictionary and will be descriptively summarized for participants in the safety population.

Antipyretic and other pain medication reported the day prior to vaccine administration will be summarized separately from the concomitant medications and for each vaccination separately.

6.6. Safety Summaries and Analyses

All safety data will be summarized according to the vaccine received for immunocompromised participants, and historical data of the age- and sex-matched healthy participants. The safety population will be used for the analysis.

6.6.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered an exploratory analysis and its purpose is to generate hypotheses for further investigation.

6.6.1.1. Related Events

AEs and SAEs deemed by the investigator to be related to the study intervention will be summarized separately. The denominator for the percentages will be the safety population.

The number and percentage of participants reporting at least 1 related (S)AE and the total number of related events may be summarized by SOC and PT. Associated 95% exact CIs will also be displayed.

6.6.1.2. Severe Events

AEs deemed severe by the investigator may be summarized separately. The denominator for the percentages will be the safety population. The number and percentage of participants reporting at least 1 severe AE and the total number of severe AEs will be reported and will be summarized by SOC and PT. Associated 95% exact CIs will also be displayed.

6.6.1.3. AEs Leading to Study Withdrawal

Any AEs leading to withdrawal from the study may be included in a participant data listing.

The percentages of AEs leading to withdrawal by immunocompromised participants and healthy controls will be presented for any AEs and by type of AEs.

As referenced in Section 5.3.1, if the withdrawal rate of Study B1971060 exceeds 15%, then an additional sensitivity analysis will be planned to study the percentage of participants who either withdraw from the study or have an AE. This is to be done descriptively to show the results separately for immunocompromised participants and healthy controls. An additional summary table could be generated to present the percentage of participants with AEs leading to study discontinuation.

6.6.1.4. Death

Any death data will be included in the study conduct summary.

6.6.2. Reactogenicity Data

Local reactions and systemic events will be summarized according to Section 6.1.2.1, Section 6.1.2.2, and Section 6.1.2.3.

6.6.3. Physical Examination

Descriptive summaries (counts and percentages) at baseline based on study intervention allocated may be provided.

7. INTERIM ANALYSES

7.1. Introduction

No interim analysis is planned for the study. Only 1 analysis will be performed at the completion of the study. The sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC will be responsible for ongoing monitoring of the safety data of participants throughout the study.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1. Agresti A. Exact small-sample inference. Chapter 1, Section 1.4.4. In: Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc; 2002:18-20.

2. Li X, Wang WWB, Liu GF, et al. Handling missing data in vaccine clinical trials for immunogenicity and safety evaluation. J Biopharm Stat. 2011;21(2):294-310.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
ACWY	*Neisseria meningitidis* serogroups A, C, W-135, and Y
AE	adverse event
bivalent rLP2086	*Neisseria meningitidis* serogroup B bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086; subfamily A and B; *Escherichia coli*)
CI	confidence interval
CRF	case report form
DMC	data monitoring committee
e-diary	electronic diary
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
ID	identification
IRT	interactive response technology
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive Web-based response system
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MenB	*Neisseria meningitidis* serogroup B
mITT	modified intent-to-treat
MnB	*Neisseria meningitidis* serogroup B
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	system organ class
WHO	World Health Organization