***ILiAD Biotechnologies***

***IB-202P***

# *A Phase 2b, Placebo-Controlled, Randomized Study of BPZE1 Intranasal Pertussis Vaccine in Healthy Adults to Assess Protection Against Colonization Following Challenge with Virulent Wild-Type Bordetella pertussis*

***30Jun2023***

Statistical Analysis Plan

**Final Version 1.0**

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## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| *B. pertussis* | *Bordetella pertussis* |
| CFU | Colony-forming units |
| CI | Confidence interval |
| eCRF | Electronic case report form |
| ELISA | Enzyme-linked immunosorbent assay |
| EOS | End of study |
| FDA | Food and Drug Administration |
| FHA | Filamentous hemagglutinin |
| FIM2/3 | Fimbriae types 2 and 3 |
| GMC | Geometric mean concentration |
| GMFR | Geometric mean fold rise |
| GMR | Geometric mean ratio |
| GMT | Geometric mean titer |
| ICE | Intercurrent event |
| ICF | Informed consent form |
| IgA | Immunoglobulin A |
| IgG | Immunoglobulin G |
| IQR | Interquartile range |
| MAD | Mucosal atomization device |
| MedDRA | Medical dictionary for Regulatory Activities |
| OTC | Over-the-counter |
| PBMC | Peripheral blood mononuclear cell |
| PCR | Polymerase chain reaction |
| PRN | Pertactin |
| PT | Pertussis toxin |
| PT | Preferred term |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SBA | Serum bactericidal assay |
| S-IgA | Secretory immunoglobulin A |
| SOC | System organ class |
| TEAEs | Treatment-emergent adverse events |
| Th | T helper cell |
| TOPS | The Overvolunteering Prevention System |
| ULN | Upper limit of normal |
| VIS | Volunteer information sheet |

# 1. Introduction

This statistical analysis plan (SAP) describes the analyses and data presentations for ILiAD's protocol IB-202P "A Phase 2b, Placebo-Controlled, Randomized Study of BPZE1 Intranasal Pertussis Vaccine in Healthy Adults to Assess Protection Against Colonization Following Challenge with Virulent Wild-Type *Bordetella pertussis*" which was issued on 03Feb2022 (amended 02Mar2022, 30May2022, 27Jul2022, and 06Mar2023). It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of colonization, immunogenicity, and safety.

The analyses for this study include one primary analysis after the last subject completes Challenge Day 16 (Visit C16) and one final analysis at the end of study (EOS). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis for the primary/final analyses. This SAP will be finalized and signed prior to the clinical database lock for the primary analyses. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.4 or higher.

This SAP is to be interpreted in conjunction with the protocol. Should the SAP and protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. If the final clinical study report (CSR) contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the CSR.

# 2. Objectives

## 2.1.Primary Objective

The primary objective is to demonstrate that prior immunization with BPZE1 protects against colonization as evidenced by a negative B. pertussis culture following virulent B. pertussis challenge 2–4 months after vaccination.

## 2.2.Secondary Objectives

### 2.2.1. Secondary Immunogenicity Objectives

- To demonstrate BPZE1 induction of mucosal anti-pertussis secretory IgA (S-IgA) antibody is improved from baseline to Day 28
- To demonstrate BPZE1 induction of systemic IgA is improved from baseline to Day 28
- To demonstrate BPZE1 induction of systemic IgG is improved from baseline to Day 28

### 2.2.2. Secondary Safety Objectives

- To assess reactogenicity profiles (by toxicity scoring) through 7 days following study vaccination
- To describe all unsolicited treatment-emergent AEs (TEAEs) through 28 days following study vaccination and following virulent challenge
- To describe all unsolicited TEAEs related to vaccination from time of vaccination to challenge or related to challenge for 3 months after challenge
- To describe any AEs of special interest (AESI) and SAEs through end of study (EOS)

### 2.3.Exploratory Objectives

- To demonstrate prior immunization with BPZE1 reduces overall bacterial load following virulent B. pertussis challenge
- To demonstrate BPZE1 induction of mucosal secretory immunity (S-IgA) and systemic immunity (IgA and IgG)
- To demonstrate BPZE1 induction of immunity is similar to that observed following virulent challenge
- To compare functional antibody response by serum bactericidal assay (SBA)
- Correlation and threshold analyses by individual and combination anti-pertussis IgG antibodies to SBA
- To assess cytokine and T helper cell (Th)1/Th2/Th17 dominance response using whole blood, peripheral blood mononuclear cells (PBMCs) and/or nasopharyngeal samples

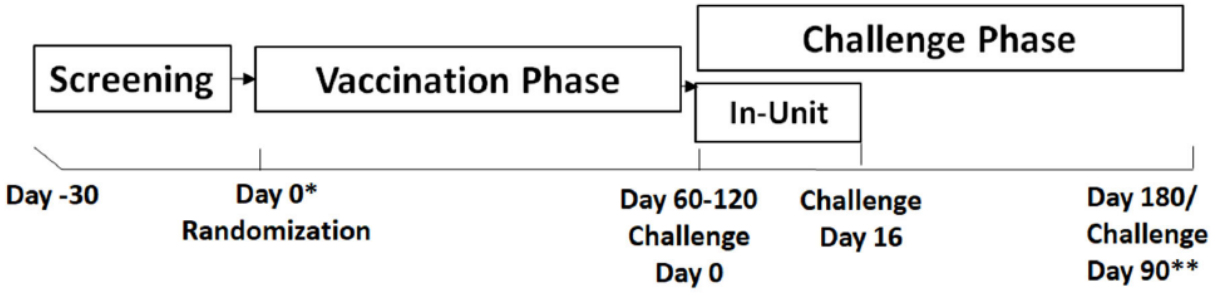
## 3. Investigational Plan

### 3.1.Overall Study Design and Plan

This is a randomized, double-blinded, placebo-controlled trial of BPZE1 that includes virulent *B. pertussis* challenge followed by a safety follow-up.

Consenting, eligible subjects will receive a single dose of BPZE1 or placebo; 2–4 months later they will be challenged with B. *pertussis* and admitted to a challenge unit. Subjects will remain in the challenge unit for a total of 17 days and 16 nights during which time they will be monitored closely. If a subject develops symptoms of pertussis, antibiotic will be started, and the subject will remain in the unit for 3 additional days of observation before discharge. If symptoms of pertussis do not develop, then subjects will receive antibiotic (azithromycin) from Days 14–16 of the challenge unit stay. Subjects will undergo safety follow-up for at least 6 months post-vaccination and at least 3 months post-challenge, for a total follow-up of 6–7 months.

**Figure 1. Dosing Scheme**




* 1:1 randomization to BPZE1 or placebo

** Subjects will be followed up to 180 days after vaccination or 90 days after virulent challenge, whichever is longer.

#### 3.1.1. Vaccination Phase

After signing the informed consent form (ICF) and meeting all inclusion and none of the exclusion criteria, a suitable number of eligible subjects (approximately 60) will be randomized 1:1 to receive BPZE1 ($10^9$ CFU) or placebo (formulation buffer) via an intranasal mucosal

atomization device (MAD) (Table 1) so that approximately 44 subjects are enrolled and challenged in the study for a minimum of 20 evaluable subjects per arm with culture results during the challenge phase, i.e., a minimum of 20 subjects per arm included in the mITT analysis set.

**Table 1. Dosing Scheme**

| Treatment Arms | Nasal Vaccination (Day 0) | | *B. pertussis* Virulent Challenge (Day 60[c]) |
|---|---|---|---|
| | BPZE1 | placebo[b] | |
| A (**N=22[a]**) | X | | X |
| B (**N=22[a]**) | | X | X |

a Evaluable subjects estimated at 20 per treatment arm with two additional to account for dropouts
b Intranasal application of 0.4 mL per nostril (0.8 mL total volume delivered) formulation buffer placebo
c Subject may enter virulent challenge unit between Days 60 to 120

On Day 0, nasal/respiratory and systemic reactogenicity will be assessed approximately 30 minutes after vaccination prior to release from clinical observation. Then, all subjects will record maximum daily reactogenicity in a subject diary for 7 consecutive days starting the day following study vaccination (retrospective of the highest value in the previous 24 hours). Both nasal/respiratory and general systemic reactogenicity events including actual measurements as needed (i.e., body temperature) will be recorded.

### 3.1.2. Challenge Phase

Between Days 60 and 120 after vaccination, subjects will plan to enter the challenge unit after confirmation to proceed to virulent challenge. Once subjects are cleared for virulent challenge, a dose of the B. pertussis strain B1917 at $10^5$ colony-forming units (CFU) will be administered while lying supine and using the procedures established within the challenge unit. Subjects will remain supine for 15 minutes. Subjects will remain in the unit for a total of 17 days for observation. Daily monitoring will occur including vital signs, physical exam (as needed), signs/symptoms of pertussis infection (e.g., catarrhal symptoms), and select clinical laboratory testing will occur on pre-specified days. Nasal washes will occur at the baseline of the challenge (Pre-Challenge) and on Challenge Days C9, C11, and C14, or prior to initiating antibiotics as well as after receiving antibiotics. If a B. pertussis culture collected on the last day of the in-unit stay (C16) is positive, the subject will return to the site to receive continued outpatient antibiotic treatment (azithromycin).

### 3.1.3. Follow-up Phase

Subjects will be followed for safety for 6 months following vaccination or 3 months following challenge, whichever is longer.

## 3.2.Study Endpoints

### 3.2.1. Primary Endpoint

The primary endpoint is the proportion of subjects by treatment group (BPZE1 and placebo) colonized on any day (Challenge Day C9, C11 or C14) following virulent challenge as determined by culture.

### 3.2.2. Secondary Endpoints

**Secondary Immunogenicity Endpoints**

- The geometric mean fold rise (GMFR) of mucosal anti-pertussis S-IgA antibody (whole cell extract [WCE], Filamentous hemagglutinin [FHA], Pertactin [PRN], Pertussis toxin [PT] and fimbriae types 2 and 3 [FIM2/3]) from baseline to Day 28 (BPZE1 and placebo). S-IgA to be normalized ([specific S-IgA]/[total S-IgA])
- The GMFR of serum IgA antibody (WCE, FHA, PRN, PT and FIM2/3) from baseline to Day 28 (BPZE1 and placebo)
- The GMFR of serum IgG antibody (WCE, FHA, PRN, PT and FIM2/3) from baseline to Day 28 (BPZE1 and placebo)

**Secondary Safety Endpoints**

- Occurrence and intensity of solicited AEs for nasal/respiratory and systemic reactogenicity through 7 days following vaccination by treatment group (BPZE1 and placebo)
- Occurrence and intensity of TEAEs through 28 days following study vaccination and following challenge by treatment group (BPZE1 and placebo)
- Occurrence and intensity of TEAEs related to vaccination from time of vaccination to challenge or related to challenge for 3 months after challenge by treatment group (BPZE1 and placebo)
- Occurrence, intensity, and relationship to study vaccine of AESIs and SAEs from vaccination through EOS by treatment group (BPZE1 and placebo)

### 3.2.3. Exploratory Endpoints

- Absolute counts (CFU/mL) in nasal wash samples on Challenge Days C9, C11 and C14 following virulent challenge by treatment group (BPZE1 and placebo)
- Geometric mean concentration (GMC)/geometric mean titer (GMT)/geometric mean ratio (GMR) of mucosal anti-pertussis S-IgA antibody, serum IgA and serum IgG antibody (WCE, FHA, PRN, PT and FIM2/3) throughout the study by treatment group (BPZE1 and placebo). S-IgA to be normalized ([specific S-IgA]/[total S-IgA])
- The GMC/GMT/GMR and GMFR of mucosal anti-pertussis S-IgA antibody, serum IgA and serum IgG antibody (WCE, FHA, PRN, PT and FIM2/3) post-vaccination and post-challenge by treatment group (BPZE1 and placebo). S-IgA to be normalized ([specific S-IgA]/[total S-IgA])
- Proportion of subjects by treatment group (BPZE1 and placebo) with a ≥2x increase in SBA 50% killing titer
- Analysis (GMC/GMT) by treatment group (BPZE1 and placebo) for each B. pertussis strain studied by SBA and by anti-pertussis IgG antibody

- Cell-mediated immunity using whole blood, PBMC and/or nasal pharyngeal samples, including but not limited to cytokines, Th1/Th17 and Th2 responses

### 3.3.Treatments

Subjects in the BPZE1 group will receive intranasal application of 2 x 0.4 mL, with 0.4 mL per nostril containing half the dose (5 x $10^8$ CFU) bacteria to give a total dose of $10^9$ CFU, via a MAD on Day 0 (Visit 1).

Subjects in the placebo group will receive an intranasal application of 2 x 0.4 mL, with 0.4 mL per nostril, reconstituted lyophilized buffer via a MAD on Day 0 (Visit 1).

The intranasal placebo consists of lyophilized buffer diluted with sterile water for injection (WFI), which are the same constituents in the same quantities as the BPZE1 investigational vaccine, except for the attenuated B. *pertussis* cells.

Once subjects are cleared for virulent challenge of a dose of the B. *pertussis* B1917 strain at $10^5$ CFU, the dose will be administered while lying supine and using the procedures established within the challenge unit. The inoculum will be instilled into each nostril with a Gilson pipette by droplet. Subjects will remain supine for 15 minutes.

## 4. General Statistical Considerations

Continuous variables will be summarized using the mean, standard deviation (SD), median, first quartile, third quartile, interquartile range (IQR), minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. All statistical tests will be two-sided at 0.05 significance level.

Baseline is defined as the last non-missing value before the vaccination on Day 0 (Visit 1). Pre-Challenge for the challenge phase is defined as the last non-missing value before the challenge on Challenge Day C0 (Visit C0).

For summary precision, mean and median will have one more decimal place than the reported value, SD will have two more decimal places than the reported value, minimum and maximum will have the same decimal place as the reported value. Percentages will have one decimal place and the 95% confidence interval (CI) will have one more decimal place than the point estimate.

For each antibody, if results are reported as lower than the minimal limit of assay detection, a value equal to half of the minimal limit of assay detection will be imputed in the calculation. The minimal limit of assay detection for each of the antibody concentrations will be established following assay qualification or validation (depending on the assay) and prior to database lock.

GMC/GMT/GMR will be calculated as anti-logarithm of $\sum$ (log-transformed concentration, titer, or ratio/number of subjects with concentration, titer or ratio information). The 95% CI for GMC/GMT/GMR will be calculated as the anti-log transformation of lower and upper limits for a two-sided 95% CI of the mean of the log-transformed titers based on normal approximation.

GMFR will be calculated as anti-logarithm of $\Sigma$ [log-transformed titer ratio of Yi/Bi)/number of subjects with titer information], where Yi is the post-dose titer and Bi is the baseline titer for subject i. GMFR over baseline and GMFR over Pre-Challenge will be calculated, if available. The same data summaries will be provided as GMC/GMT/GMR.

For immunogenicity analysis, it is assumed that the natural log of the data is normally distributed.

All data collected will be listed in data listings.

### 4.1.Sample Size

Table 2 depicts the power for the challenge study as computed under the following assumptions: two-sided significance level of 0.05, use of a likelihood ratio test for testing equality of two proportions, a sample size of 20 in each of the two groups, a colonization rate of 60%, 70%, and 80% in the unvaccinated group and colonization rates of 10%, 20%, 30%, and 40% in the vaccinated group.

Sample sizes of 20 evaluable subjects in each group achieve a power of at least 90% to detect differences between colonization rates of at least 50% in six scenarios. These scenarios include the following colonization rates for the placebo and BPZE1 groups, respectively: 60% versus 10%, 70% versus 10%, 70% versus 20%, 80% versus 10%, 80% versus 20% and 80% versus 30%, which are bolded in Table 2.

**Table 2. Power for Sample Sizes of 20 in Each Group for Varying Colonization Rates Based on a Likelihood Ratio Test**

| **Colonization Rate** | | | |
|---|---|---|---|
| **Placebo** | **BPZE1** | **N/group** | **Power** |
| | | | |
| 60% | **10%** | 20 | 94% |
| | 20% | | 75% |
| | 30% | | 48% |
| | 40% | | 24% |
| | | | |
| 70% | **10%** | 20 | 99% |
| | **20%** | | 92% |
| | 30% | | 73% |
| | 40% | | 48% |
| | | | |
| 80% | **10%** | 20 | 100% |
| | **20%** | | 99% |
| | **30%** | | 92% |
| | 40% | | 75% |

Table 3 includes results based on vaccine efficacy computed from the colonization rates in each population, rather than comparing the two colonization rates and testing the null hypothesis that they are equal in the two populations. The computations presented in the table below are based on a normal approximation. The table includes the required sample size for a power of 80% and for lower bounds of vaccine efficacy of 0%, 10%, 20%, and 30%. For a colonization rate of 70% in the placebo group and a lower bound of efficacy of 20%, the study will be powered for

efficacy rates of 71% or higher. Focusing on an efficacy rate greater than 50% and a lower bound of 0% or higher (sample sizes in bold), the study is well powered to detect efficacy rates of 57% or higher.

**Table 3. Estimated Sample Size Based on Assumed Colonization rates and Power of 80% and Lower Bounds of 0%, 10%, 20% and 30%**

| Colonization rate | | Sample size/group | | | | |
|---|---|---|---|---|---|---|
| **Control** | **Vaccine** | **Efficacy** | **LB 0%** | **LB 10%** | **LB 20%** | **LB 30%** |
| 60% | 10% | 0.833 | **11** | **12** | **14** | **18** |
| | 20% | 0.667 | **18** | 22 | 29 | 42 |
| | 30% | 0.500 | 33 | 47 | 75 | 149 |
| | 40% | 0.333 | 77 | 141 | 390 | 5675 |
| | | | | | | |
| 70% | 10% | 0.857 | **8** | **9** | **10** | **12** |
| | 20% | 0.714 | **12** | **14** | **18** | 24 |
| | 30% | 0.571 | **19** | 25 | 36 | 60 |
| | 40% | 0.429 | 33 | 51 | 95 | 268 |
| | | | | | | |
| 80% | 10% | 0.875 | **6** | **6** | **7** | **9** |
| | 20% | 0.750 | **8** | **9** | **12** | **16** |
| | 30% | 0.625 | **12** | **15** | **20** | 31 |
| | 40% | 0.500 | **18** | 25 | 40 | 82 |

For the endpoint of absolute counts, the standard deviation in the BPZE1 group was computed to be 2.2 for the natural log of the counts and 4.2 for the natural log of the counts in the control group. Assuming a sample size of 20 evaluable subjects in each group, a two-sample t-test accounting for unequal variances, and a two-sided significance level of 0.05, the study has approximately 80% power to detect differences of 3.1 units or larger between the BPZE1 group and the control group on the natural log scale.

### 4.2.Randomization and Blinding

Subjects will be randomized in a 1:1 ratio to receive BPZE1 or placebo. Unblinded individuals at the site will use the randomization list generated by the Biostatistics randomization team to allocate the subjects to either BPZE1 or placebo. All vaccinated subjects will be invited to Challenge phase. Per protocol, subjects who withdraw, are withdrawn due to an unrelated AE as determined by the Investigator, are lost to follow-up prior to the challenge phase, or subjects who miss all 3 culture results (Challenge Days C9, C11 and C14) during the challenge phase may be replaced. The randomization schedule with leading number “1” (1001-1088) is the main randomization number. The randomization schedule with leading number “2” (2001-2088) is the replacement randomization number. Replacement randomization schedule is the identical treatment arm with the main randomization schedule (i.e., the treatment arm of 1001 and 2001

are identical). If a randomized subject is deemed to be replaced, the Investigator will assign the replacement randomization number to the subject to ensure the replacement subject is in the same treatment arm with the subject being replaced.

Subjects who decline to receive the challenge agent can remain in the study to participate in safety follow-up visits after vaccination. An unblinded statistician not associated with the study team will review the randomization assignment to ensure that a minimum of 20 evaluable subjects per arm are included in the mITT analysis set.

This is a double-blind study. Neither the subject nor the Investigator/site staff will know what study vaccine the subject is receiving with the exception of site staff involved in the preparation of the vaccination. These members of staff will take no further part in the study.

The site(s) will identify an unblinded individual(s) who will be provided with a randomization list. This list will be used to allocate the subjects to either BPZE1 or placebo. To maintain the blind, unblinded individuals will only be involved in vaccine logistics and preparation. The unblinded team will not be involved in any study-related assessments or have subject contact for data collection following study vaccination. Blinded individuals will administer the study vaccine with further details in the Pharmacy/Challenge Manual.

Code break envelopes will be provided to the site(s) so that they can unblind an individual subject in the event of a medical emergency. Where possible they should discuss the situation with the Sponsor's medical monitor prior to unblinding; however, the subject's safety must always come first. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

## 4.3.Analysis Set

### 4.3.1. Safety Analysis Set

The safety analysis set will consist of all subjects randomized to treatment who are vaccinated. Subjects will be classified according to the actual vaccine received. The safety analysis will be done on this analysis set.

### 4.3.2. Intent-to-Treat (ITT) Analysis Set

The intent-to-treat analysis set will consist of all subjects randomized to treatment who are vaccinated. Subjects will be classified according to the randomized treatment group.

### 4.3.3. Modified Intent-to-Treat (mITT) Analysis Set

The modified intent-to-treat analysis set will consist of all subjects randomized to treatment who are vaccinated, challenged, and have at least one culture result at Challenge Day C9, C11, or C14. Subjects will be classified according to the randomized treatment group.

### 4.3.4. Adequate Inoculum Analysis Set

The adequate inoculum analysis set will consist of all subjects who are included in the mITT analysis set and received a challenge inoculum of $\geq 5 \times 10^4$ CFU on Challenge Day C0.

### 4.3.5. Per Protocol (PP) Analysis Set

The per-protocol analysis set will consist of all subjects who are included in mITT population with no major protocol deviations. This wording has been updated from the protocol definition.

### 4.4.Handling of Missing Data

Colonization data will be presented in the listings as reported. For summaries and analysis, the following conventions apply.

When only one day out of three days (Challenge Days C9, C11 and C14) is missing:

- If Day C9 and Day C11 are negative but Day C14 is missing, Day C14 will be imputed as negative;
- If Day C9 and Day C14 are negative but Day C11 is missing, Day C11 will be imputed as negative;
- Because participants are closely monitored in the challenge unit, it is deemed highly unlikely that they will miss Day C9 but come back for Days C11 and Day C14, therefore the scenario of missing Day C9 only is not considered;
- If any day is positive, the remaining missing data will not be imputed.

When two days out of three days (Challenge Days C9, C11 and C14) are missing:

- If Day C9 is negative but Day C11 and Day C14 are missing, Day C11 and Day C14 will be imputed as negative;
- As described above, it is deemed highly unlikely that participants will miss an earlier assessment but come back for later day assessment, including the following two scenarios:
  - Day C11 is negative but Day C9 and Day C14 are missing
  - Day C14 is negative but Day C9 and Day C11 are missing

  therefore both scenarios are not considered.
- Data may also be missing due to the sample being corrupt.
- If any day is positive, the remaining missing data will not be imputed.

**Impute Missing Adverse Events/ Prior or Concomitant Medications**

**A. <u>Incomplete Start Date:</u>**

*Missing day and month*

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.

- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

*Missing day only*

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date, i.e. set to the stop date.

*Missing day, month, and year*

- No imputation is needed; the corresponding AE will be included as TEAE if the end date of the AE is after the first dosing date or the end date is also missing.

**B. <u>Incomplete End Date:</u>**

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

*Missing day and month*

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

*Missing day only*

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date

is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

### 4.5.Analysis Window/Visit

Visit windows are defined in Section 13.1. Additionally, analysis windows will be derived using the following rules:

**Table 4. Analysis windows**

| Study Phase | Study Visit/Study Day | Analysis Window |
|---|---|---|
| Vaccination Phase | Visit 1/Day 0 | No analysis window allowed |
| | Visit 2/Day 7 | Day 5 to Day 21 |
| | Visit 3/Day 28 | Day 22 to Day 45 |
| | Visit 4/Day 52[a] | Day 46 to Day 120 |
| Challenge Phase | Visit C0 to C16/Day 0-16[b] | No analysis window allowed[d] |
| Safety Follow-up | Visit 5/Day 28[b] | Challenge Day 21 to Challenge Day 89 |
| | EOS/Day 180[c] | Challenge Day 90 to Challenge Day 120 (EOS) |

a Initiate screening for eligibility for the Challenge Phase; admit to challenge unit on Study Visit C0
b Days relative to Challenge Phase
c This visit will occur at least 6 months post-vaccination or at least 3 months post-challenge
d The analysis window for Challenge Day 9, 11 and 14 refers to table 5.

## 5. Subject Disposition

### 5.1.Disposition

The number of subjects who were randomized and screen failed will be presented based on all screened subjects.

Disposition of all randomized subjects (ITT Analysis Set and mITT Analysis Set) will be summarized by treatment groups and overall including:

- Number of subjects vaccinated
- Number of subjects never vaccinated
- Number of subjects received challenge agent
- Number of subjects who completed challenge unit
- Reasons for not completing challenge unit
    - Adverse Event

  - Withdrawal of Consent
  - Other
- Number of subjects never challenged
  - Number of subjects discontinued from the study before challenge
  - Primary reasons for study discontinuation before challenge
    - Lost to Follow-Up
    - Withdrawal of Consent by Subject
    - Investigator Decision
    - Adverse Event
    - Death
    - Significant Noncompliance with Protocol
    - Sponsor Decision
    - Other
  - Number of subjects who did not receive challenge but participated in safety follow-up
  - Reasons for not receiving challenge agent after receiving study vaccine
    - Adverse Event
    - Withdrawal of Consent
    - Sponsor Decision
    - Other
- Number of subjects who completed study (EOS)
- Number of subjects who prematurely discontinued study
- Primary reason for premature discontinuation of study

Primary reasons for study discontinuation collected on the Study Termination eCRF will be summarized with the following categories:

- Lost to Follow-Up
- Withdrawal of Consent by Subject
- Investigator Decision
- Adverse Event
- Death
- Significant Noncompliance with Protocol
- Sponsor Decision
- Other

Number of subjects in each analysis set will also be summarized in disposition table.

Reasons for ITT subject excluded from mITT analysis set will be summarized with the following categories:

- Missing Colonization Culture (Challenge Days C9, C11, or C14)
- Not Challenged

The subjects who did not receive challenge but completed the safety follow-up will be considered as Completed Study.

A by-subject disposition listing will be provided based on the ITT Analysis set. Eligibility criteria met/failed for vaccination phase and challenge phase will be listed based on all screened subjects.

### 5.2.Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the agreed procedures or processes. Deviations will be assessed with Sponsor involvement and deemed significant or non-significant prior to database lock.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Significant protocol deviations will be summarized using the ITT Analysis Set.

A by-subject listing will be provided based on the ITT Analysis Set including both the significant and non-significant protocol deviations.

## 6. Demographics and Baseline Characteristics

### 6.1.Demographics

Demographic and baseline characteristics data to be analyzed will include age, sex, ethnicity, weight, height, and body mass index (BMI) on the ITT analysis set, mITT analysis set, Adequate Inoculum analysis set, and Per-Protocol analysis set by treatment group and overall.

The following characteristics will be summarized and presented as continuous variables:

- Age (years)
- Weight (kg)
- Height (cm)
- BMI ($kg/m^2$)

The following characteristics will be summarized and presented as categorical variables:

- Sex (Male, Female)
- Ethnicity (White, Black, Asian, Mixed or Multiple ethnic groups, Other)

A by-subject listing will be provided based on the ITT Analysis set.

## 6.2.Medical History

Medical history will be summarized based on the ITT Analysis Set and mITT Analysis Set and will be coded according to latest version of Medical Drug Regulatory Activities (MedDRA). Medical history will be summarized by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC in descending order of frequency.

A by-subject listing will be provided for medical history based on the ITT Analysis set.

# 7. Treatments and Medications

## 7.1.Prior and Concomitant Medications

The Anatomical Therapeutic Chemical (ATC) coding scheme of the latest World Health Organization Drug Dictionary (WHODrug) will be used to group medications into relevant categories.

### 7.1.1. Prior Medications

Prior medications are defined as non-study medications with a start date before the date of vaccination. Prior medications that continue on and after the date of vaccination will be reported as both prior and concomitant medications. Prior medications will be summarized based on the ITT Analysis Set and mITT Analysis Set by ATC2 level and preferred medication names, with ATC2 level sorted alphabetically and preferred names within each ATC2 level in descending order of frequency.

A by-subject listing will be provided for prior medications based on the ITT Analysis Set.

### 7.1.2. Concomitant Medications

Concomitant medications are defined as all medications and over-the-counter (OTC) products, including herbals, supplements, vaccines, and multivitamins, taken by the subject from the time of vaccination through the EOS visit, or through an early termination visit, if prior to these time points.

Concomitant medications will be summarized by ATC2 level and standardized medication names, with ATC2 level sorted alphabetically and standardized names within each ATC2 level in descending order of frequency. Summaries will be provided based on the Safety Analysis Set.

A by-subject listing will be provided for concomitant medications based on the Safety Analysis set.

### 7.1.3. Concomitant Vaccination

Vaccines received outside of the study will be specifically queried during each visit and recorded through EOS. Concomitant vaccinations will be summarized based on Safety Analysis Set.

A by-subject listing will be provided for concomitant vaccinations based on the Safety Analysis set.

### 7.2.Study Treatments

Number of days from vaccination to receiving challenge agent will be summarized using descriptive statistics based on the mITT Analysis Set.

A by-subject listing will be provided based on the All Randomized subjects for receiving vaccination and receiving challenge agent.

## 8. Efficacy Analysis

Unless otherwise specified, efficacy analysis will be performed based on the mITT Analysis Set. All summaries and analyses will be presented over all subjects and by treatment groups.

By subject listings will be provided for pertussis antigen specific antibody titer using mucosal samples, pertussis antigen specific antibody titer using serum sample, colonization *B. pertussis* Bacterial Culture, and cellular response based on ITT Analysis Set.

The visit windows to be used for the definition of the primary endpoint of colonization are provided in Table 5.

**Table 5. Visit windows for endpoint of colonization**

| Visit | Window |
|---|---|
| Challenge Day 9 | Challenge Day 8, 9 or 10 |
| Challenge Day 11 | Challenge Day 11, 12 |
| Challenge Day 14 | Challenge Day 13, 14 |

### 8.1.Primary Efficacy Analysis

The estimand description for the primary efficacy analysis is provided in Table 6.

**Table 6. Estimand attributes for the primary efficacy analysis**

| **Estimand Label** | Estimand |
|---|---|
| **Estimand Description** | The difference in the proportion of colonization on any day (Challenge Day C9, C11, or C14) following virulent Challenge agent (*B. pertussis* B1917 strain at $10^5$ CFU) on Challenge Day C0 between BPZE1 and placebo administered intranasally via a MAD in healthy adult subjects 2-4 months prior to challenge |
| **Target population** | All healthy adult subjects who receive vaccination, are challenged, and have at least one culture result at Challenge Day C9, C11, or C14. |
| **Treatment Condition** | Trial arm: BPZE1 (2 x 0.4 mL (0.4 mL per nostril containing half the dose (5 x $10^8$ CFU) of bacteria to give a total dose of $10^9$ CFU) administered intranasally via a MAD) on Day 0<br>Control arm: Placebo (2 x 0.4 mL (0.4 mL per nostril) reconstituted lyophilized buffer administered intranasally via a MAD) on Day 0<br>Challenge: a $10^5$ CFU dose of the *B. pertussis* strain B1917 on Challenge Day C0 |
| **Endpoint** | The proportion of subjects by treatment group (BPZE1 and placebo) colonized on any day (Challenge Day C9, C11 or C14) following virulent challenge as determined by culture. |
| **Population-level summary** | Difference between the proportion of subjects colonized on any day (Challenge Day C9, C11, or C14) in the BPZE1 group and the placebo group. |
| **Intercurrent Events and Strategies** | |
| **ICE1 (discontinued prior to challenge or prior to Challenge Day C9 culture)** | Subjects may be replaced. |

| | |
|---|---|
| **ICE2 Missing culture(s)** | (a) Single missing culture<br>• If Day C9 and Day C11 are negative but Day C14 is missing, Day C14 will be imputed as negative;<br>• If Day C9 and Day C14 are negative but Day C11 is missing, Day C11 will be imputed as negative;<br>Because participants are closely monitored in the challenge unit, it is deemed highly unlikely that they will miss Day C9 but come back for Days C11 and Day C14; the scenario of missing Day C9 only will not be considered<br>(b) Two missing cultures<br>• If Day C9 is negative but Day C11 and Day C14 are missing, Day C11 and Day C14 will be imputed as negative;<br>• As described above, it is deemed highly unlikely that participants will miss an earlier assessment but come back for later day assessment, including the following two scenarios:<br>a. Day C11 is negative, but Day C9 and Day C14 are missing<br>b. Day C14 is negative, but Day C9 and Day C11 are missing<br>Both Scenarios will not be considered.<br>(c) Positive culture at any of Challenge Days C9, C11, and C14 in the presence of missing cultures<br>When this is the case, the result will be considered positive. |
| **ICE3 (protocol deviations)** | Treatment Policy |
| **ICE4 (prohibited medications)** | Treatment Policy |

A subject is defined to be colonized if the culture result is positive. The number and proportion of subjects colonized on any of the three days - Challenge Days C9, C11, or C14 will be summarized by treatment group. The two-sided 95% CIs for each treatment group will be computed using the Agresti-Coull method, and the 95% CIs for the difference in proportions between the BPZE1 group and the placebo group will be computed using Agresti-Caffo method. The colonization counts and proportions in the BPZE1 and placebo groups will be summarized for each of Challenge Days C9, C11, and C14 using same method.

To assess the primary objective, the following superiority hypothesis will be tested on the proportion of subjects colonized on any of the days (Challenge Days C9, C11 or C14) following challenge.

Test hypothesis for superiority:

$$H_0: P_1 \geq P_2$$

$$H_1: P_1 < P_2$$

where,

$P_1$ = proportion of subjects colonized on any of the days (Challenge Days C9, C11 or C14) following challenge in BPZE1 group

$P_2$ = proportion of subjects colonized on any of the days (Challenge Days C9, C11 or C14) following challenge in placebo group

Superiority of BPZE1 will be declared if $P_1 < P_2$ and the two-sided P-value is less than 0.05 for the likelihood ratio chi-square test. If 25% of the cells have expected counts that are less than 5, a Fisher's exact test will be performed.

Analysis will be conducted on mITT Analysis Set.

### 8.1.1. Sensitivity Analysis for the Primary Efficacy Analysis

Sensitivity analyses will be performed on the Adequate Inoculum Analysis Set and Per Protocol Analysis Set separately following the same analysis method described above in Section 8.1.

An additional sensitivity analysis will use a logistic regression model with treatment group, denoted as 1 for BPZE1 and 0 for placebo, and inoculum count as covariates, with colonization status (any day of Challenge Day C9, C11, or C14) as the outcome (modelling the response of not being colonized). The null hypothesis will be tested using the coefficient associated with treatment group. The odds and 95% CI, and odds Ratio (BPZE1 vs. placebo) and 95% CI and p-value will be provided.

Results for the mITT, Adequate Inoculum, and Per Protocol analysis sets will be summarized in a forest plot. Results from the logistic regression will also be summarized in a forest plot.

## 8.2.Secondary Efficacy Analysis

### 8.2.1. GMFR of Mucosal Anti-pertussis S-IgA Antibody from Baseline to Day 28

The GMFR and GMC/GMR, as well as the corresponding 95% CIs, for mucosal S-IgA for each of the anti-pertussis antibodies (WCE, FHA, PRN, PT and FIM2/3) at Visit 3/Day 28 will be provided by treatment group. A paired t-test will be used to test the null hypothesis of no change from baseline to Visit 3/Day 28 in log-transformed anti-pertussis mucosal secretory IgA (S-IgA) antibody levels within both the BPZE1 group and placebo group and a two-sided p-value will be provided. The 95% CI for the GMFRs within both the BPZE1 group and placebo group for the changes from baseline to Visit 3/Day 28 of the log-transformed mucosal S-IgA will be constructed based on normal approximation. The 95% CI will be transformed back to the original data scale by exponentiating the values.

Mucosal S-IgA will be normalized as [specific S-IgA]x100/[Total S-IgA] and it will also be summarized using same method.

Analyses will be based on mITT Analysis Set.

### 8.2.2. GMFR of Serum IgA Antibody from Baseline to Day 28

The GMFR and GMC, as well as the corresponding 95% CIs for serum IgA for each of the anti-pertussis antibodies (WCE, FHA, PRN, PT and FIM2/3) at Visit 3/Day 28, will be provided by treatment group. The same approach described in Section 8.2.1 for the GMFR of Mucosal Anti-pertussis S-IgA Antibody from baseline to Visit 3/Day 28 will be applied.

Analyses will be based on mITT Analysis Set.

### 8.2.3. GMFR of Serum IgG Antibody from Baseline to Day 28

The GMFR and GMC, as well as the corresponding 95% CIs for Serum IgG for each of the anti-pertussis antibodies (WCE, FHA, PRN, PT and FIM2/3) at Visit 3/Day 28, will be provided by treatment group. The same approach described in Section 8.2.1 for the GMFR of Mucosal Anti-pertussis S-IgA Antibody from baseline to Visit 3/Day 28 will be applied.

Analyses will be based on mITT Analysis Set.

### 8.2.4. Sensitivity Analysis for the Secondary Efficacy Analysis

Sensitivity analyses will be performed on the ITT Analysis Set, Adequate Inoculum Analysis Set and Per Protocol Analysis Set separately following the same analysis method described in Sections 8.2.1, 8.2.2, and 8.2.3.

An additional ANCOVA model will be fit with the outcome being the change from baseline to Day 28 in natural log scale (i.e., GMFR in natural log scale), baseline value in natural log scale, treatment group, and inoculum count in natural log scale as covariates.

Results for the mITT, ITT, Adequate Inoculum, and Per Protocol analysis sets will be summarized in a forest plot.

Results from the ANCOVA models will also be summarized in a forest plot.

## 8.3.Exploratory Efficacy Analysis

Unless otherwise stated, all analyses described in this Section will be performed on the mITT analysis set and Adequate Inoculum Analysis Set.

### 8.3.1. Absolute Colony Counts in Nasal Wash Samples on Challenge Days C9, C11 and C14 Following Virulent Challenge by Treatment Group

Absolute colony counts (colony forming unit per mL, CFU/mL) in nasal wash samples on Challenge Days C9, C11, and C14 following virulent challenge will be summarized using descriptive statistics by treatment group and by timepoint. Geometric means and corresponding 95% CIs will be provided.

Reverse cumulative distribution curves will be provided for nasal wash samples on Challenge Days C9, C11 and C14 Following Virulent Challenge by Treatment Group.

### 8.3.2. GMC/GMR of Mucosal Anti-pertussis S-IgA Antibody, Serum IgA and Serum IgG Antibody Throughout the Study by treatment group

The GMC/GMR with the 95% CI for mucosal S-IgA, Serum IgA, and Serum IgG for each of anti-pertussis antibodies (WCE, FHA, PRN, PT and FIM2/3) throughout the study will be provided by treatment group by timepoint. S-IgA will be provided both as specific mucosal S-IgA and normalized using [specific S-IgA]x100/[total S-IgA].

A two-sample t-test will be used to compare the log-transformed GMCs/GMRs between the BPZE1 group and placebo group at each timepoint and a two-sided p-value will be provided. In addition, the difference of the log-transformed GMCs/GMRs between the BPZE1 and placebo groups will be calculated and the 95% CIs for the differences will be constructed based on the normal approximation. To transform back to the original data scale as the 95% CI for ratio of two GMCs/GMRs, the upper and lower limits of the 95% CI will be exponentiated.

Reverse cumulative distribution curves will be provided for Mucosal anti-pertussis S-IgA Antibody at baseline, Visit 3/Day 28, Visit 4/C-1, Visit 5/C28, and Visit 6/EOS based on ITT and mITT analysis sets.

Reverse cumulative distribution curves will be provided for Serum IgA and Serum IgG Antibody at baseline, Visit 3/Day 28, Visit C0, Visit 5/C28, and Visit 6/EOS based on ITT and mITT analysis sets.

### 8.3.3. GMC/GMR and GMFR of Mucosal Anti-pertussis S-IgA Antibody, Serum IgA and Serum IgG Antibody Post-vaccination and Post-challenge by Treatment Group

The GMC/GMR with the 95% CI for mucosal S-IgA, Serum IgA, and Serum IgG for each of the anti-pertussis antibodies (WCE, FHA, PRN, PT and FIM2/3) at baseline, Visit 3/Day 28, Visit 4/C-1 or Visit C0, Visit 5/C28, and Visit 6/EOS, will be provided by treatment group and timepoint. S-IgA will be provided both as specific mucosal S-IgA and normalized using [specific S-IgA]x100/[total S-IgA]. Visit 3/Day 28 will be considered as post-vaccination. Visit 5/C28 will be considered as post-challenge.

A two-sample t-test will be used to compare the log-transformed GMCs/GMRs between the BPZE1 and placebo groups at each timepoint and a two-sided p-value will be provided. In addition, the difference of the log-transformed GMCs/GMRs between the BPZE1 and placebo groups will be calculated and the 95% CI for the difference will be constructed based on the normal approximation. To transform back to the original data scale as the 95% CI for ratio of two GMCs/GMRs, the lower and upper limits of the 95% CI will be exponentiated.

The GMFR for mucosal S-IgA, Serum IgA, and Serum IgG for each of the anti-pertussis antibodies (WCE, FHA, PRN, PT and FIM2/3) at Visit 3/Day 28, Visit 4/C-1 or Visit C0, Visit 5/C28, and Visit 6/EOS will be provided by treatment group and timepoint.

The 95% CI for the GMFRs in the BPZE1 group and placebo group of the log-transformed mucosal S-IgA, Serum IgA, and Serum IgG for each of the anti-pertussis antibodies (WCE, FHA, PRN, PT, and FIM2/3) will be constructed based on normal approximation. To transform back to the original data scale, the lower and upper limits of the 95% CI will be exponentiated.

Two-sample t-tests will be used to compare the log-transformed GMFRs post-vaccination (Visit 3/Day 28 over baseline) and post-challenge (Visit 5/C28 over Visit 4/C-1 or Visit C0) between the BPZE1 and placebo groups and two-sided p-values will be provided. In addition, the

95% CI will be constructed based on normal approximation. To transform back to the original data scale as the 95% CI for ratio of two GMFRs, the lower and upper limits of the 95% CI will be exponentiated.

### 8.3.4. Proportion of Subjects by Treatment Group with a ≥2x Increase in SBA Bactericidal Titer

The number and proportion of subjects with a ≥2x increase from baseline in SBA bactericidal titer (50% killing titre) will be summarized by treatment group and by strain. The 95% CIs for each treatment group will be computed using the Agresti-Coull method and the 95% CIs for the difference in proportions between the BPZE1 group and the placebo group will be computed using Agresti-Caffo method. A chi-square test will be performed to compare the proportion of subjects between two treatment groups with a ≥2x increase in SBA bactericidal titer and two-sided p-value will be provided.

### 8.3.5. Analysis of Treatment Group for Each B. pertussis Strain Studied by SBA and by Anti-pertussis IgG Antibody

The GMT with the 95% CI for SBA and Anti-pertussis IgG Antibody for each B. *pertussis* strain will be provided by treatment group. Correlation analyses will be conducted between SBA (PRN+ and PRN-) and anti-pertussis IgG antibody (WCE, PRN, FHA, PT, and FIM2/3) levels by B. *pertussis* strain and timepoint using either Pearson's Correlation coefficient or Spearman's Rho depending on the normality of the sample distribution.

Reverse cumulative distribution curves will be provided for SBA (PRN+ and PRN-) at baseline, Visit 3/Day 28, Visit C0, Visit 5/C28, and Visit 6/EOS based on ITT and mITT analysis sets.

### 8.3.6. Cell-mediated Immunity Using Whole blood, PBMC and/or Nasal Pharyngeal Samples

The mean with 95% CI for cell-mediated immunity using PBMC, whole blood, and/or nasal pharyngeal samples, including but not limited to cytokines, Th1/Th17 and Th2 responses will be provided by treatment group and timepoint.

Reverse cumulative distribution curves will be provided for cell-mediated immunity using PBMC, whole blood, and/or nasal pharyngeal samples by treatment group based on ITT and mITT analysis sets.

## 9. Safety Analysis

Unless otherwise specified, safety analysis will be performed based on the Safety Analysis Set. All summaries and analyses will be presented over all subjects and by treatment groups (BPZE1, placebo, and Total).

### 9.1.Solicited Adverse Events

The number and percentage of subjects with any solicited AEs (nasal/respiratory and systemic reactogenicity events) through 7 days following study vaccination will be calculated by treatment group.

Solicited reactogenicity events occurring through 7 days following study vaccination, including nasal/respiratory reactions and systemic reactions, will be summarized as number and frequency by reactogenicity grades (Table 7).

If subjects have fever in 7 days following vaccination, the oral temperature will be measured and will be summarized using descriptive statistics.

Duration through 7 days following study vaccination and duration through resolution following study vaccination will be summarized using descriptive statistics. Duration through 7 days is defined as days with the reactogenicity event onset through 7 days following vaccination per patient reported daily diary. Duration beyond 7 days is defined as days with the reactogenicity event continuing beyond 7 days as captured in adverse events.

Solicited nasal/respiratory and systemic adverse events will be presented in data listings.

**Table 7. Reactogenicity Grading Scale**

| **Nasal/Respiratory/Systemic Reactogenicity Grading** | | | |
|---|---|---|---|
| **Reaction** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
| Runny nose | Noticeable but does not interfere with daily activity | Moderate discomfort that interferes with daily activity | Significant discomfort/prevents daily activity or seeks medical care |
| Stuffy nose/congestion | Noticeable but does not interfere with daily activity | Moderate discomfort that interferes with breathing from nose | Unable to breathe through nose or seeks medical care |
| Nasal pain/irritation | Noticeable but does not interfere with daily activity | Moderate discomfort that interferes with daily activity | Significant discomfort that prevents daily activity or seeks medical care |
| Epistaxis | Total duration of all episodes in a 24-hour period <30 minutes | Total duration of all episodes in a 24-hour period >30 minutes | Any bleeding that required visit for medical encounter |
| Sneezing | Noticeable but does not interfere with daily activity | Moderate discomfort that interferes with daily activity | Significant discomfort; prevents daily activity |
| Sinus pressure/pain | Noticeable but does not interfere with daily activity | Moderate discomfort that interferes with daily activity | Significant discomfort that prevents daily activity or seeks medical care |
| Sore/irritated throat | Noticeable but does not interfere with eating or drinking | Moderate discomfort that interferes with eating or drinking | Significant discomfort that prevents eating or drinking or seeks medical care |
| Cough | Noticeable but does not interfere with daily activity or sleeping | Frequent cough that interferes with daily activity or sleeping | Prevents daily activity, prevents sleep, or seeks medical care |
| Shortness of breath/wheezing | Noticeable but does not interfere with daily activity | Moderate discomfort that interferes with daily activity | Significant discomfort/ prevents daily activity or seeks medical encounter |
| Fever | 100.4–101.1°F | 101.2–102.0°F | >102°F |

| Nasal/Respiratory/Systemic Reactogenicity Grading | | | |
|---|---|---|---|
| **Reaction** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
| | (38.0–38.4°C) | (38.5–38.9°C) | (≥39.0°C) |
| Fatigue (tiredness) | No interference with daily activity | Some interference with daily activity | Significant interference, prevents daily activity |
| Malaise (general unwell feeling) | No interference with daily activity | Some interference with daily activity | Significant interference, prevents daily activity |
| Myalgia (body aches/muscular pain) | No interference with daily activity | Some interference with daily activity | Significant interference, prevents daily activity |
| Arthralgia (joint pain) | No interference with daily activity | Some interference with daily activity | Significant interference, prevents daily activity |
| Headache | No interference with daily activity | Some interference with daily activity | Significant interference, prevents daily activity |
| Rash/hypersensitivity | Pruritus OR local rash | Diffuse rash | Diffuse rash with blisters or mouth ulcerations, anaphylaxis, or angioedema |

Source: Modified based on Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov). Accessed 26 April 2022.Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. July 2017 [cited 26 April 2022]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

## 9.2.Unsolicited Adverse Events

Unsolicited AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) latest version. Unless otherwise specified, unsolicited AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT), with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of subject incidence.

A TEAE is defined as an AE that occurs after the subject has been vaccinated. AEs will be summarized by treatment groups and overall and by study phase (vaccination phase and challenge phase). All AESIs and SAEs will be monitored from signing of informed consent through to the EOS visit. All AEs regardless of causality will be recorded for 28 days after vaccination and 28 days after challenge. All AEs related either to vaccination or to challenge will be collected from time of vaccination to challenge and for 3 months after challenge, respectively.

### 9.2.1. Incidence of Adverse Events

An overview summary of the following TEAE categories by treatment group and total will be provided:

- Any TEAE
- Any TEAE from Vaccination Phase Day 29 to prior to Challenge
- Any TEAE from Challenge Phase Day 29 to EOS
- Any TEAE related to vaccination
- Any TEAE related to MAD
- Any TEAE related to challenge

- Any severe TEAE
- Any serious TEAE
- Any serious TEAE related to vaccination
- Any serious TEAE related to MAD
- Any serious TEAE related to challenge
- Any AESI
- Any AESI related to vaccination
- Any AESI related to MAD
- Any AESI related to challenge
- Any TEAE leading to study discontinuation
- Any TEAE leading to death

### 9.2.2. Relationship of Adverse Events to Study Vaccination/Challenge

The relationship of vaccination to TEAE will be characterized using the following criteria:

- Related to vaccination: there is a reasonable possibility that the study vaccination caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study vaccination and the AE
- Not related to vaccination: there is not a reasonable possibility that the administration of the study vaccination caused the event
- Related to challenge agent: there is a reasonable possibility that the challenge agent caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study vaccination and the AE
- Not related to challenge agent: there is not a reasonable possibility that the administration of the challenge agent caused the event

All TEAEs through 28 days following study vaccination and following challenge will be summarized by relationship to study vaccination/challenge/MAD, SOC/PT and by treatment group.

### 9.2.3. Severity of Adverse Event

The severity of the AE will be rated as mild, moderate, or severe using the following criteria:

- Mild/Grade 1: these events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate/Grade 2: these events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.
- Severe/Grade 3: these events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

If a subject reports multiple occurrences of a specific event, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used.

All TEAEs through 28 days following study vaccination and following challenge will be summarized by SOC/PT and severity, and by treatment group.

TEAEs related to vaccination from time of vaccination to challenge and TEAEs related to challenge for 3 months after challenge will be summarized by severity and SOC/PT, and by treatment group.

### 9.2.4. Serious Adverse Events

An SAE is defined as any event that:

- results in death
- is life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious TEAE will be summarized by severity and SOC/PT and by treatment group, and by relationship separately.

A by-subject listing will be provided.

### 9.2.5. Adverse Events of Special Interest

An AESI is defined as adverse events related to infection with or vaccination for SARS-CoV-2 and will be collected on a unique eCRF through to the EOS.

All AESIs will be summarized as number and percentage by severity and SOC/PT and by treatment group, and by relationship separately.

A by-subject listing will be provided.

### 9.2.6. Adverse Events Leading to Study Discontinuation

TEAEs leading to study discontinuation will be summarized by SOC/PT and by treatment group.

A by-subject listing will also be provided.

### 9.2.7. Death

A by-subject listing will also be provided for all AEs leading to death.

### 9.2.8. Pre-defined Post-Challenge Checklist

During the in-unit period the volunteers will be reviewed at least twice per day (once in the morning and once in the evening) following a standardised checklist including body temperature, respiratory rate, heart rate, and early symptoms of pertussis: rhinorrhoea, nasal congestion, epistaxis, sneezing, ear pain, eye pain, sore throat, cough, dyspnoea, feeling generally unwell, tiredness and headache. The pre-defined post-challenge checklist will be summarized using descriptive statistics by treatment group and overall.

A by-subject listing will be provided for all pre-defined post-challenge checklist.

## 9.3.Clinical Laboratory Evaluations

Subjects with values meeting FDA toxicity criteria (Table 8) will be summarized by grade and treatment group. Only abnormal laboratory values were collected.

A by-subject listing will be provided for abnormal laboratory results.

## Table 8. Table for Laboratory Grading

| **Serum**[a] | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)**[b] |
|---|---|---|---|---|
| Glucose – hyperglycemia Random (mg/dL; mmol/L) | 110–125 (6.1–<7.0) | 126–200 (7.0–11.1) | >200 (>11.1) | Insulin requirements or hyperosmolar coma |
| Blood Urea Nitrogen (mg/dL; mmol/L) | 23–26 (8.2–9.5) | 27–31 (9.6–11.1) | >31 (>11.1) | Requires dialysis |
| Creatinine (mg/dL; umol/L) | 1.5–1.7 (133–154) | 1.8–2.0 (155–180) | 2.1–2.5 (181–225) | >2.5 (>225) or requires dialysis |
| Albumin – hypoalbuminemia (g/dL; g/L) | 2.8–3.1 (28–31) | 2.5–2.7 (25–27) | <2.5 (<25) | – |
| Total Protein – hypoproteinemia (g/dL; g/L) | 5.5–6.0 (55–60) | 5.0–5.4 (50–54) | <5.0 (<50) | – |
| Liver Function Tests – ALT, AST increase by factor | 1.1–2.5 x ULN | 2.6–5.0 x ULN | 5.1–10 x ULN | >10 x ULN |
| Bilirubin – when accompanied by any increase in liver function test; increase by factor | 1.1–1.25 x ULN | 1.26–1.5 x ULN | 1.51–1.75 x ULN | > 1.75 x ULN |
| Bilirubin – when liver function test is normal; increase by factor | 1.1–1.5 x ULN | 1.6–2.0 x ULN | 2.0-3.0 x ULN | > 3.0 x ULN |
| **Haematology**[a] | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)**[b] |
| Haemoglobin (Female) (g/dL; g/L) | 11.0–12.0 (110–120) | 9.5–10.9 (95–109) | 8.0–9.4 (80–94) | <8.0 (<80) |
| Haemoglobin (Male) (g/dL; g/L) | 12.5–13.5 (125–135) | 10.5–12.4 (105–124) | 8.5–10.4 (85–104) | <8.5 (<85) |
| WBC elevation (cell/$mm^3$; $x10^9$/L) | 10,800–15,000 (10.8–15) | 15,001–20,000 (>15–20) | 20,001–25,000 (>20–25) | >25,000 (>25) |
| WBC suppression (cell/$mm^3$; $x10^9$/L) | 2500–3500 (2.5–3.5) | 1500–2499 (1.5–<2.5) | 1000–1499 (1.0–<1.5) | <1,000 (<1.0) |
| Platelets Decreased (cell/$mm^3$; $x10^9$/L) | 125,000–140,000 (125–140) | 100,000–124,000 (100–124) | 25,000–99,000 (25–99) | <25,000 (<25) |

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; WBC=white blood cell.

a The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

b The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125–129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value

Note: Screening laboratory samples with toxicity scores greater than 1 are exclusion criteria for vaccination enrolment. Laboratory sampling while in the challenge unit will comply with challenge unit standard protocol with the proviso that concurrent evidence of illness requires a daily complete blood count with differential to be conducted.

Source: Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov). Accessed April 26, 2022.

### 9.3.1. Pregnancy Test

Serum and/or urine will be collected from female subjects of childbearing potential at the times outlined in the Schedule of Events (Section 13.1) to enable pregnancy test.

Only a by-subject listing will be provided for serum/urine pregnancy test.

### 9.3.2. COVID-19 Testing

COVID-19 testing will be performed at the times outlined in the Schedule of Events (Section 13.1).

Only a by-subject listing will be provided for COVID-19 testing.

## 9.4.Vital Sign Measurements

Vital sign measurements will include body temperature (oral, tympanic, or noncontact), heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation, and will be collected at the times outlined in the Schedule of Events (Section 13.1), pre-vaccination and pre-challenge and approximately 30 minutes following vaccination and challenge, respectively, and any unscheduled visits. During the challenge unit stay, vital signs will be collected at least twice daily (once in the morning and once in the evening). Temperature will also be recorded daily in a subject diary for 7 consecutive days starting the day following study vaccination.

Vital sign measurements will be summarized using descriptive statistics for reported values and change from baseline at each scheduled visit. Shift from baseline results will be presented in pre- versus post-treatment cross-tabulations, with classes for mild, moderate, and severe, as indicated in Table 9.

A by-subject listing will be provided.

**Table 9. Table for Vital Sign Grading**

| Vital signs | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially life threatening (Grade 4) |
|---|---|---|---|---|
| Fever (°C) | 38.0–38.4 | 38.5–38.0 | >39.0 | >40.0 |
| Tachycardia (bpm) | 101–115 | 116–130 | >130 | Emergency room visit or hospitalised for arrhythmia |
| Bradycardia (bpm) | 50–54 | 45–49 | <45 | Emergency room visit or hospitalised for arrhythmia |
| Hypertension (systolic) mmHg | 141–150 | 151–155 | >155 | Emergency room visit or hospitalised for malignant hypertension |
| Hypertension (diastolic) mmHg | 91–95 | 96–100 | >100 | Emergency room visit or hospitalised for malignant hypertension |
| Hypotension (systolic) mmHg | 85–89 | 80–84 | <80 | Emergency room visit or hospitalised for hypotensive shock |

Bpm=beats per minute
a Subject should be at rest for all vital sign measurements
b Oral temperature; no recent hot or cold beverages or smoking
c When resting heart rate is between 60 to 100 bpm. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes
Note: Grade 0 will be the classification if the observation is less than a Grade 1. Respiratory rate was removed from the FDA table for vital sign grading as this is not a parameter being measured in this study
Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov). Accessed April 26, 2022.

### 9.5.Physical Examination

A full physical examination will be done at Screening visit and pre-challenge. A targeted physical examination will be assessed at the times outlined in the Schedule of Events (Section 13.1), including unscheduled visits. Height and weight will be measured at the screening and pre-challenge visits only.

Height, weight, and BMI will be summarized using descriptive statistics for reported values and change from baseline at each scheduled visit.

A by-subject listing will be provided for all physical examination data.

## 10. Primary Analysis

Primary analysis will be performed at the time when all subjects completed Challenge phase (Challenge Day C16).

## 11. Changes in the Planned Analysis

Not applicable.

## 12. References

Modified based on Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov). Accessed 26 April 2022.Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. July 2017 [cited26 April 2022]. Available from:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov). Accessed April 26, 2022.

# 13. Appendices

## 13.1. Schedule of Events

| | | Vaccination Phase | | | | Challenge Phase | | | | | | | Safety Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Screening** | **1** | **2** | **3** | **4/C-1[a]** | **C0** | **C1-6[b]** | **C7** | **C8, C10, C12 & C13[b]** | **C9, C11 & C14[b]** | **C15** | **C16** | **5** | **6** |
| **Days Relative to Vaccination[c]** | **-30 to -7** | **0** | **7** | **28** | **52** | **---** | **---** | **---** | **---** | **---** | **---** | **---** | **---** | **180/EOS[q]** |
| **Days Relative to Challenge** | | | | | **-7[r]** | **0** | **1-6** | **7** | **8, 10, 12, and 13** | **9, 11 and 14** | **15** | **16** | **28** | **90[q]** |
| **Window Allowance[c]** | **30** | **NA** | **+3** | **+7** | **+60** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **+7** | **+30** |
| VIS/Informed consent/TOPS registration | X | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | X | | | | | | | | |
| Infection control agreement | X | | | | | X | | | | | | | | |
| Demographic and baseline data | X | | | | | | | | | | | | | |
| Medical history | X | X | | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs | X | X[d] | X | X | | X[d] | X | X | X | X | X | X | X | X |
| Physical examination | X[e] | X | X | X | | X[e] | X | X | X | X | X | X | X | X |
| Serology and anti-PT and anti-PRN Ab (local and central lab) | X | | | | | | | | | | | | | |
| Safety laboratory samples | X | | | | X | | | X | | X (C9 and C14 only) | | | | |

| | | Vaccination Phase | | | | Challenge Phase | | | | | | | Safety Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Screening** | **1** | **2** | **3** | **4/C-1[a]** | **C0** | **C1-6[b]** | **C7** | **C8, C10, C12 & C13[b]** | **C9, C11 & C14[b]** | **C15** | **C16** | **5** | **6** |
| **Days Relative to Vaccination[c]** | **-30 to -7** | **0** | **7** | **28** | **52** | **---** | **---** | **---** | **---** | **---** | **---** | **---** | **---** | **180/EOS[q]** |
| **Days Relative to Challenge** | | | | | **-7[r]** | **0** | **1-6** | **7** | **8, 10, 12, and 13** | **9, 11 and 14** | **15** | **16** | **28** | **90[q]** |
| **Window Allowance[c]** | **30** | **NA** | **+3** | **+7** | **+60** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **+7** | **+30** |
| Respiratory PCR panel | | | | | | X[p] | | | | | | | | |
| Urine toxicity screen | X | | | | X | | | | | | | | | |
| Serum pregnancy test (FCBP only) | X | | | | | | | | | | | | | |
| Urine pregnancy test (FCBP only) | | X | | | | X | | | | | | | | |
| 12-lead electrocardiogram | X | | | | | | | | | | | | | |
| SARS-CoV-2 test for active infection[f] | | X | | | | X | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | |
| Vaccination | | X | | | | | | | | | | | | |
| Challenge | | | | | | X | | | | | | | | |
| Subject diary dispensing[g] | | X | | | | | | | | | | | | |
| Reactogenicity/Solicited AEs[g] | | X[g,h] | X | | | | | | | | | | | |
| Post-challenge checklist | | | | | | X | X | X | X | X | X | X | | |
| Subject diary or checklist reviewed[i] | | | X | | | X | X | X | X | X | X | X | | |
| Azithromycin | | | | | | | | | | X (C14 only)[j] | X | X[j] | | |
| Nasal wash for *B. pertussis* colonization by culture ± PCR | | | | | X | | | | | X | | X[k] | X | |

| | | Vaccination Phase | | | | Challenge Phase | | | | | | | Safety Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Screening** | **1** | **2** | **3** | **4/C-1[a]** | **C0** | **C1-6[b]** | **C7** | **C8, C10, C12 & C13[b]** | **C9, C11 & C14[b]** | **C15** | **C16** | **5** | **6** |
| **Days Relative to Vaccination[c]** | **-30 to -7** | **0** | **7** | **28** | **52** | **---** | **---** | **---** | **---** | **---** | **---** | **---** | **---** | **180/EOS[q]** |
| **Days Relative to Challenge** | | | | | **-7[r]** | **0** | **1-6** | **7** | **8, 10, 12, and 13** | **9, 11 and 14** | **15** | **16** | **28** | **90[q]** |
| **Window Allowance[c]** | **30** | **NA** | **+3** | **+7** | **+60** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **+7** | **+30** |
| Nasopharyngeal swab(s) for cell-mediated immunity | X | | X | X | X | | | | | X (C9 only) | | | X | |
| Nasal mucosal secretion sample (SAM) for immunogenicity test | X | | | X | X | | | | | | | | X | X |
| Serum for immunogenicity (including ELISA and SBA assays) | | X[l] | | X | | X[l] | | | | | | | X | X |
| Blood sampling for cellular-mediated immunity | | X[l] | X | X | | X[l] | | X | | | | | X | |
| All unsolicited AEs[m] | | X | X | X | | X | X | X | X | X | X | X | X | |
| TEAEs related to vaccination[n] | | X | X | X | X | | | | | | | | | |
| TEAE related to challenge[n] | | | | | | X | X | X | X | X | X | X | X | X |
| AESIs and SAEs[o] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

AE=adverse event; AESI=adverse event of special interest; ELISA=enzyme-linked immunosorbent assay; EOS=end of study; FCBP=female(s) of childbearing potential; PCR=polymerase chain reaction; SAE=serious adverse event; SBA=serum bactericidal assay; TEAE=treatment emergent adverse event

a. Initiate screening for eligibility for the Challenge Phase; admit to challenge unit on Study Visit C0
b. Each day has the same assessments, unless specified
c. Days relative to vaccination are only estimates as the window allowances are not inclusive. Subjects will remain in the study until either 6 months after vaccination or 3 months after challenge, whichever is longer. If a study pause occurs, the visits/windows will be adjusted to allow for subjects to continue without protocol deviation.

d. Pre-vaccination and approximately 30 minutes following vaccination and challenge; additional vital sign measurements to be taken per challenge unit as needed
e. Full physical examination including height and weight at Screening and Study Visit C0. Symptom-directed (targeted) physical examination at all other scheduled time points. Interim physical examinations will be performed at the discretion of the Investigator, if necessary
f. SARS-CoV-2 testing should be performed within approved national guidelines with tests that are approved through a (minimum) of emergency use authorization. Minimally invasive testing should be considered for the comfort of subjects. Subjects need to have negative test results within 72 hours prior to vaccination and admission to the challenge unit. Repeat testing is allowed on multiple occasions, if needed
g. All subjects will record maximum daily reactogenicity/solicited AEs in the subject diary for the subsequent 7 days after vaccination. Subjects will be instructed that should they have reactogenicity with a potential toxicity grade 3 at any time after vaccination, they should contact the site on the same day and be seen or referred to a qualified medical facility
h. Immediate reactogenicity will be assessed 30 minutes after the study vaccination, prior to release from clinical observation
i. Site staff reviews the information from the subject diary/checklist with the subjects to confirm accuracy. For reactogenicity and post-challenge checklist, the appropriate FDA toxicity grading should be applied. If any reactogenicity event extended beyond 7 days post-vaccination and is deemed clinically significant by AE classification, then it should be entered as an AE (graded by AE criteria) with the same start date as the reactogenicity event and followed to resolution. All AEs identified by the post-challenge checklist should be entered as an AE
j. Prior to Study visit C14, azithromycin may be initiated if subjects have symptoms consistent with pertussis, although assessments listed for C14 should be carried out prior to starting azithromycin. On Study visit C14, all subjects who have not yet started azithromycin should begin a 3-day course of azithromycin 500 mg per day after all study samples have been collected; the third dose of azithromycin must be taken prior to the subject exiting the challenge unit on Study visit C16
k. Subjects with positive culture or PCR sampled on C16 will be required to return to the challenge unit to receive additional antibiotic treatment
l. Collect prior to vaccination/challenge
m. All unsolicited AEs to be collected from time of vaccination to 28 days after vaccination and from time of challenge to 28 days after challenge
n. Treatment-related AEs due to vaccination and due to challenge to be collected from time of vaccination to challenge and then for 3 months after challenge, respectively
o. All AESIs and SAEs to be collected from time of signed informed consent to EOS
p. Maybe performed at the discretion of the Investigator throughout the Challenge Phase
q. This visit will occur at least 6 months post-vaccination or at least 3 months post-challenge
r. Visit may occur up to 8 days before C0 or as close to C0 as possible to allow availability of test results.

# Statistical Analysis Plan (SAP) Client Approval Form

| | |
|---|---|
| **Client:** | ILiAD Biotechnologies, LLC |
| **Protocol Number:** | IB-202P |
| **Document Description:** | Final Statistical Analysis Plan |
| **SAP Title:** | A Phase 2b, Placebo-Controlled, Randomized Study of BPZE1 Intranasal Pertussis Vaccine in Healthy Adults to Assess Protection Against Colonization Following Challenge with Virulent Wild-Type Bordetella pertussis |
| **SAP Version Number:** | 1.0 |
| **Effective Date:** | 30JUN2023 |

## Author(s):

**For PPD:** Pu Huang, Biostatistician II

## Approved by:

Xinayi Kong, Biostatistics Director
Biostatistics & Programming, CRG

Date *(DD-MMM-YYYY)*

Stephanie Noviello, Global Clinical Lead,
ILiAD Biotechnologies

30-JUN-2023
Date *(DD-MMM-YYYY)*

# Statistical Analysis Plan (SAP) Client Approval Form

| | |
|---|---|
| **Client:** | ILiAD Biotechnologies, LLC |
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| | |
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| **SAP Version Number:** | 1.0 |
| **Effective Date:** | 30JUN2023 |

## Author(s):

**For PPD:** Pu Huang, Biostatistician II

## Approved by:

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Xianyi Kong
Signer Name: Xianyi Kong
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Xinayi Kong, Biostatistics Director
Biostatistics & Programming, CRG

Date *(DD-MMM-YYYY)*

Stephanie Noviello, Global Clinical Lead,
ILiAD Biotechnologies

Date *(DD-MMM-YYYY)*

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