# A Phase 2 Multicenter, Randomized, Active-Controlled, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 25-Valent Pneumococcal Conjugate Vaccine in Healthy PCV-Naïve Adults

**CONFIDENTIAL**

**March 6, 2024**

**Sponsored by:**
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USA

**Version 4.0**

## Confidentiality Statement

# LIST OF ABBREVIATIONS AND ACRONYMS

| ABBREVIATION/ ACRONYM | DEFINITION |
|---|---|
| Ab | antibody |
| ADR | adverse drug reaction |
| AE | adverse event |
| alum | aluminum as aluminum phosphate |
| ALT | alanine transaminase |
| AST | aspartate aminotransferase |
| ATC | anatomical therapeutic chemical |
| bpm | beats/breaths per minute |
| CI | Confidence interval |
| CMO | Chief Medical Officer |
| CONSORT | Consolidated Standards of Reporting Trials |
| $CRM_{197}$ | Cross Reactive Material 197 |
| CRO | contract research organization |
| DMP | Data Management Plan |
| DSMB | Data and Safety Monitoring Board |
| EC | ethics committee |
| EDC | electronic data capture |
| ELISA | enzyme-linked immunosorbent assay |
| EPI | Expanded Programme on Immunisation |
| FA | full analysis |
| Gavi | Gavi, The Vaccine Alliance |
| GCP | Good Clinical Practice |
| GMC | Geometric Mean Concentration |
| GMFR | Geometric Mean Fold Rise |
| GMR | Geometric Mean Ratio |
| GMT | geometric mean titer |
| GSK | GlaxoSmithKline |
| HepB/HB | Hepatitis B virus |
| HBsAg | Hepatitis B virus surface antigen |
| HCV | Hepatitis C virus |
| Hgb | hemoglobin |
| HIV | human immunodeficiency virus |
| HZ | hydrazide |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| ID | identification |
| IgG | immunoglobulin G |
| IPD | invasive pneumococcal disease |
| IRT | Interactive response technology |
| IVT PCV-25 | 25-valent candidate pneumococcal conjugate vaccine manufactured by |

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| | Inventprise, Inc. |
| IWRS | Interactive Web Response System |
| LLOQ | lower limit of quantification |
| LMIC | low- and middle-income countries |
| LSLV | last participant last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MO | Medical Officer |
| MOPA | multiplexed opsonophagocytic assay |
| NML | National Microbiology Laboratory |
| NRA | national regulatory authority |
| NZW | New Zealand White |
| OPA | opsonophagocytic assay |
| ORA | Office of Research Affairs |
| PCV | pneumococcal conjugate vaccine |
| PE | physical examination |
| PEG | polyethylene glycol |
| PFS | pre-filled syringe |
| PI | Principal Investigator (the term is used throughout to indicate PI or designee) |
| Plts | platelets |
| PP | per protocol |
| PSRT | Protocol Safety Review Team |
| PQ | prequalification |
| PT | Preferred Term |
| RCD | reverse cumulative distribution |
| REB | Research Ethics Board |
| SAE | serious adverse event |
| SD | standard deviation |
| SOC | System Organ Class |
| SOP | standard operating procedure |
| SSP | study specific procedure |
| T bili | total bilirubin |
| TEN | Toxic epidermal necrolysis |
| TMF | Trial Master File |
| TRS | Technical Report Series |
| UK | United Kingdom |
| ULOQ | upper limit of quantification |
| USA | United States of America |
| WBC | white blood cell |
| WHO | World Health Organization |
| WCG IRB | Western Institutional Review Board |
| WOCBP | women of childbearing potential |
| 2-PE | 2-phenoxyethanol |

# STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- Canada Food and Drug Regulations applicable to clinical studies (Part C, Division 5)
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Good Clinical Practice (GCP) E6
- World Medical Association Declaration of Helsinki – Ethical Principles for Research Involving Human Participants (Oct 2013 or subsequent amendments)

# PROTOCOL SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH-GCP guidelines as outlined in the 'Statement of Compliance.'

Sponsor Date

Name: Sybil Tasker, M.D. MPH
Title: Chief Medical Officer
Organization: Inventprise, Inc.

# KEY ROLES AND CONTACT INFORMATION

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|---|---|
| **Sponsor** | Inventprise, Inc.<br>18133 NE 68th St, D150<br>Redmond, Washington 98052 USA |
| **Implementing Partner** | PATH<br>2201 Westlake Avenue, Suite 200<br>Seattle, WA 98121 USA |
| **Vaccine Manufacturer** | Inventprise, Inc.<br>18133 NE 68th St, D150<br>Redmond, Washington 98052 USA |
| **Contract Research Organization(s)** | [redacted] |
| **Immunology Laboratories (Pneumococcal Serology)** | [redacted] |

# PROTOCOL SUMMARY

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| **TITLE** | A Phase 2 Multicenter, Randomized, Active-Controlled, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 25-Valent Pneumococcal Conjugate Vaccine in Healthy PCV-Naïve Adults |
| **STUDY NUMBER** | CVIA 105 |
| **PROJECT PHASE** | Phase 2 |
| **INVESTIGATIONAL PRODUCT(S)** | **Investigational Vaccine:**<br>Three formulations of Pneumococcal 25-valent conjugate vaccine (IVT PCV-25).<br>Formulation A: [redacted]<br>Formulation B: [redacted]<br>Formulation [redacted]<br>**Active Comparator Vaccine:**<br>Pneumococcal 20-valent conjugate vaccine (conjugated to $CRM_{197}$ carrier protein) suspension for intramuscular injection (Prevnar 20™). |
| **HYPOTHESES** | IVT PCV-25 will have an acceptable safety and tolerability profile in adults.<br>IVT PCV-25 will be immunogenic and will elicit seroresponses to the serotypes present in the candidate vaccine. |

| OBJECTIVES | ENDPOINTS | ESTIMANDS |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| 1. To describe the reactogenicity, tolerability, and safety of IVT PCV-25 administered as a single-dose regimen to healthy pneumococcal vaccine-naïve adults. | 1. Local reactions (redness, swelling, and pain at the injection site)<br>2. Systemic events (fever, headache, fatigue, muscle pain, joint pain, and rash)<br>3. Unsolicited Adverse events (AEs)<br>4. Serious adverse events (SAEs) | **Population**: Healthy pneumococcal vaccine-naïve adult participants receiving study vaccines<br>**Population-level summary:**<br>1. Number and severity of solicited local reactions within 7 days after vaccination (redness, swelling, and pain at the injection site) by group<br>2. Number and severity of solicited systemic AEs within 7 days after vaccination by group<br>3. Number and severity of unsolicited AEs within 28 days after vaccination by group<br>4. Number of SAEs within 6 months after vaccination by group |
| **Secondary:** | **Secondary:** | **Secondary:** |
| 1. To describe the immune responses elicited by a single dose of IVT PCV-25 against the 25 serotypes contained in IVT PCV-25 (1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, 35B) as well as serotype 6A, alone and in comparison to the antibody responses against these serotypes induced by Prevnar 20$^{TM}$ in healthy adults | 1. Serotype-specific immunoglobulin G (IgG) antibody responses<br>2. Serotype-specific functional antibody responses measured by Opsonophagocytic Assay (OPA) | **Population:** Healthy pneumococcal vaccine-naïve adult participants receiving study vaccines, complying with the key protocol criteria, and providing evaluable sample at baseline and 28 days after vaccination<br>**Population-level summary:**<br>1. Geometric mean concentrations (GMC) of serotype-specific IgG at each time point (Day 1 and Day 29) by group<br>2. Geometric mean fold rise (GMFR) in serotype-specific IgG GMCs from baseline to Day 29 after vaccination by group<br>3. Percentage of participants achieving a $\geq$4-fold IgG rise from baseline to Day 29 after vaccination by group<br>4. Ratio of GMCs between IVT PCV-25 and Prevnar 20 groups 28 days after vaccination |

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|---|---|---|
| | | 5. Ratio of IgG GMFR between IVT PCV-25 and Prevnar 20 groups<br>6. Geometric mean titers (GMTs) of serotype-specific OPA antibodies at each time point (Day 1 and Day 29) by group<br>7. Geometric mean fold rise (GMFRs) in serotype-specific OPA GMTs from baseline to Day 29 after vaccination by group<br>8. Ratio of GMTs between IVT PCV-25 and Prevnar 20 groups 28 days after vaccination<br>9. Ratio of OPA GMFR between IVT PCV-25 and Prevnar 20 groups |

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| **STUDY RATIONALE** | The bacterium *Streptococcus pneumoniae* (the pneumococcus) kills approximately 300,000 children annually before their fifth birthday, mostly in low-resource areas of the world. The most common cause of childhood morbidity and mortality is pneumonia, which in 2019 was estimated to be the cause of roughly 740,000 under-five deaths worldwide, making it one of the deadliest infectious diseases of young children today. Although pneumonia has multiple bacterial and viral etiologies, *S. pneumoniae* is the leading cause of severe pneumonia. In addition to pneumonia, *S. pneumoniae* also causes a number of other serious invasive diseases, including sepsis and meningitis, and mucosal diseases, such as otitis media, which collectively result in significant morbidity and mortality. The highest incidence of invasive pneumococcal disease (IPD) is seen at the extremes of age, in the elderly and children less than 5 years old. Public health leaders agree that vaccines are the best way to address the enormous burden of pneumococcal disease, particularly in Africa and Asia, where 95% of all pneumococcal deaths occur.<br><br>Since their first introduction in 2000, the first-generation (7-valent Prevnar®) and subsequent second-generation (10-valent Synflorix® and 13-valent Prevnar 13®) pneumococcal conjugate vaccines (PCVs) have resulted in a significant reduction in the incidence of vaccine-type IPD, not only in vaccinated infants and young children but also in non-vaccinated adults due to herd immunity. The second-generation PCVs were developed to address the increasing burden of disease caused by newly emergent non-vaccine ('replacement') serotypes after 7-valent PCV introduction. However, not only have these vaccines been less effective than the 7-valent PCV in addressing vaccine-type disease (with roughly 30% of cases of IPD in children < 5 years still due to Prevnar 13® serotypes in Canada in 2019), |

there has been a significant increase in non-vaccine-type IPD since their introduction due to additional replacement serotypes, underscoring the need for development of third-generation PCVs of higher valency.

In addition to these issues concerning their overall efficacy, the second-generation PCVs, like their predecessor, are complicated and expensive to produce, making them difficult for low-income countries to afford without considerable external financial assistance. Low- and middle-income countries (LMICs) that do not qualify for financial support can rarely afford these vaccines within their health budgets.

To address these issues, Inventprise Inc. has partnered with PATH (a global health organization based in Seattle, Washington) to develop a safe, effective and low-cost third-generation PCV vaccine that is designed to prevent IPD due to the remaining predominant serotypes causing disease in children, particularly those residing in Africa and other low- and middle-income regions of the world. This same vaccine will also be made available in high income regions. The resulting candidate vaccine (IVT PCV-25) contains capsular polysaccharides from 25 pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, and 35B.

[redacted]

[redacted]he IVT PCV-25 vaccine thus has the potential to not only significantly broaden coverage against disease-causing serotypes but may also have increased efficacy against the serotypes contained in Prevnar 13®, including problematic serotypes such as 19A and 3 eliciting low immune responses.

[redacted]

The IVT PCV-25 vaccine was recently tested in a randomized, active-controlled, observer-blind, Phase 1 study (CVIA 096) to evaluate the safety, tolerability, and immunogenicity in adults (NCT05540028) at the Canadian Center for Vaccinology, Dalhousie University, IWK Health Centre Halifax, Nova Scotia, Canada. This single dose IVT PCV-25 vaccine was administered to 60 adults, age 18-40 years, and randomized 1:1 to the

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| | comparator PCV Prevnar 20™. [redacted]<br><br>The Data and Safety Monitoring Board (DSMB) reviewed the safety data after the single dose immunization in the 60-person adult cohort (NCT05540028) through Day 29 and determined that the reactogenicity and safety were favorable and approved moving forward in age de-escalation prior to the Sponsor's decision to suspend the trial. No SAEs occurred, and Grade 3 AEs were determined to be unrelated to investigational product(s). The adult cohort [redacted] will continue safety follow-up through study end (Day 169, estimated July 2023) for all 60 adult participants enrolled in the study, after which the study will be terminated.<br><br>This Phase 2 trial of IVT PCV-25 is designed to provide the necessary assurances of safety, reactogenicity, and immunogenicity of a single dose of three different dose-ranging formulations of IVT PCV-25 in order to proceed directly to infants for a dose-finding Phase 2 trial. [redacted] |
| **STUDY DESIGN** | In this prospective, multicenter, randomized, active-controlled, observer-blind Phase 2 study, 220 adult (age 18-49 years) eligible participants will be randomized to four groups as shown below (Table 1). The four groups will be conducted concurrently and randomized in a 2:3:4:2 ratio. The rationale for sample size, dose selection, and interim analysis is provided in the clinical protocol Section 1.8. |

**Table 1. Randomization Scheme**

| Group | n | [redacted] | |
|---|---|---|---|
| Group A | 40 | | |
| Group B | 60 | | |
| Group C | 80 | | |
| Group D | 40 | Prevnar 20™ comparator | |

[redacted]

For all participants, eligibility to participate in the study, including assessment of medical history, vital signs and physical examination, will be undertaken after the participant signs the informed consent form (ICF).

Each adult will undergo a total of 4 clinic visits (V), including at least one screening visit (V0) not more than 28 days prior to Day 1 (V1), a vaccination visit on Day 1 (V1), follow-up clinic visits at 7 (+3) and 28 (+7) days post-vaccination (V2 and V3, respectively) as shown in Table 2. Daily local and systemic reactogenicity will be monitored during the 7 days after vaccination (Day 1 and following 6 days) by memory aid. Blood will be collected for hematological and biochemical laboratory tests at screening (V0) and Day 8 (V2). Blood will be collected at baseline (V1) and 28 days post-vaccination (V3) to assess serotype-specific IgG antibody and OPA functional antibody responses in all participants. There will be a final follow-up call on Day 169 (V4).

**Table 2. Study Schedule**

| Groups | Visits/Study Day | | | | |
|---|---|---|---|---|---|
| | **Screening (D0)** | **V1 (D1)** | **V2 (D8)** | **V3 (D29)** | **V4 (D169)** |
| | -28 to 0 | 1 | V1+7 (+3) | V1+28 (+7) | V1+168 (+14) |
| IVT PCV-25 Group A | B* | B, X | B* | B | — |
| IVT PCV-25 Group B | B* | B, X | B* | B | — |
| IVT PCV-25 Group C | B* | B, X | B* | B | — |
| Prevnar 20™ Group D | B* | B, X | B* | B | — |

B = blood draw (serum); X = study vaccination

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| | *Blood draw for clinical laboratory tests<br><br>An independent DSMB will review unblinded safety data after the last participant completes the 28-day follow-up visit (V3).<br><br>There will be three analyses. The first analysis, aka interim analysis, will be conducted once all subjects have completed the Day 29 visit and will include all safety data through Day 29 from all 220 participants and available immunogenicity data at the time of clinical database freeze which is estimated to be from approximately 50% or more of the participants, The goal of the first analysis is to enable rapid advancement of the program into the target pediatric population by assessing safety, and excluding formulations that are clearly insufficiently immunogenic. The Sponsor plans to submit to Health Canada the report from this first analysis in order to inform early planning for a follow-on dose-ranging Phase 2 trial in infants.<br><br>The Sponsor and its consultants, PATH, and representatives from the Bill & Melinda Gates Foundation will review both group-level and individual-level (with participant ID masked) serotype-specific IgG antibody responses (baseline and Day 29) from the interim analysis, and the group-level unblinded safety data to ensure that both the safety profile and the immune responses to IVT PCV-25 are sufficient to proceed to planning for a Phase 2 study in infants. The Investigators will be provided the group-level safety and immunogenicity results. All site and CRO personnel will remain blinded to individual treatment assignment until end of study.<br><br>The second analysis will be conducted once serotype-specific OPA data from the baseline and Day 29 visits from all 220 participants become available and will include both group-level and individual-level (with participant ID-masked) serotype-specific OPA results. The unblinded group-level second analysis will be shared with the Sponsor and its consultants, PATH, the Investigators, and representatives from the Bill & Melinda Gates Foundation. The individual-level, participant ID-masked results will be shared with the Sponsor and its consultants, PATH, and representatives from the Bill & Melinda Gates Foundation as they become available.<br><br>The third and final analysis will include all late safety events from all participants through Day 169 (end of study) with the complete IgG and OPA immunogenicity results from all participants. |
| **SAFETY MONITORING** | The Principal Investigators and Sub-Investigators will provide continuous monitoring of all study participants' safety. All participants will be assessed for the following:<br><br>• Local and systemic reactogenicity at 30 (+10) min post-vaccination |

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| | • Local and systemic reactogenicity during the first 7 days after vaccination by memory aid<br>• Unsolicited AEs for 28 days post-vaccination by memory aid<br>• SAEs throughout the entire study period.<br>• The number, severity, and relatedness of clinically significant hematological and biochemical measurements at 7 days post-vaccination will be assessed.<br><br>Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.<br>**Pause Rules:**<br>**Rule 1**: 1 or more participant experiences any vaccine-related Grade 4 AE or any vaccine-related SAE.<br><br>**Rule 2**: 1 or more participant experiences the following Grade 3 or greater local reaction classified as related to vaccination by the PI: ulceration, necrosis, or sterile abscess at the injection site requiring drainage or surgical intervention.<br><br>**Rule 3**: ≥ 5 participants in the same group inclusive of participants from Groups A, B, C, and D that experience the same Grade 3 (or greater) AE or laboratory abnormality attributed (related) to study vaccine. In the case of fever and pain at the injection site, the episode must last longer than 48 hours, and, in the case of fever, be confirmed by the PI without evidence of other medical causes. |
| **STUDY POPULATION** | Four concurrent groups of healthy adults aged 18 to 49 years (N = 220) residing in Canada will be enrolled in the study, with randomization (Visit 1) as follows:<br><br>Randomization ratio: 2:3:4:2<br><br>Group A: 40 participants<br>Group B: 60 participants<br>Group C: 80 participants<br>Group D: 40 participants |
| **PARTICIPANT DURATION** | Participant participation will be up to 7 months (including screening), and the total study duration is anticipated to be approximately 10 months depending upon the estimated enrollment period. |

## BACKGROUND AND RATIONALE

### 1.1 Burden of Disease

According to the Global Burden of Disease Study 2016 [1] the bacterium *Streptococcus pneumoniae* kills approximately 300,000 children before their fifth birthday annually, mostly in low-resource areas of the world. The most common cause of childhood morbidity and mortality due to the bacterium is pneumonia, which in 2019 was estimated to be the cause of roughly 740,000 under-five deaths worldwide, making it the most deadly infectious disease of young children today [2]. Although pneumonia has multiple bacterial and viral etiologies, *S. pneumoniae* is the leading cause of severe pneumonia. In addition to pneumonia, *S. pneumoniae* also causes a number of other serious invasive diseases, including sepsis and meningitis, and mucosal diseases, such as otitis media, which collectively result in tremendous morbidity and mortality. The highest incidence of invasive pneumococcal disease (IPD) is seen at the extremes of age, in adults ≥ 65 years and children < 5 years of age [3]. Public health leaders agree that vaccines are the best way to address the enormous burden of pneumococcal disease, particularly in Africa and Asia, where 95% of all pneumococcal deaths occur [4].

### 1.2 Pathogen and Clinical Disease

*S. pneumoniae* is a Gram-positive encapsulated organism that is commonly carried as a commensal in the human nasopharynx. More than 100 serotypes of the bacterium have been identified based on differences in the composition of its polysaccharide capsule, which is an essential virulence factor. Pneumococci are transmitted by direct contact with respiratory secretions from infected individuals and healthy carriers. Children commonly harbor one or more strains and become carriers during the first few years of life [5]. Carriage is typically asymptomatic; however, it is believed to be a precondition for invasive pneumococcal infection [6].

### 1.3 Licensed Pneumococcal Conjugate Vaccines

In 1983, Pneumovax® 23, a pneumococcal polysaccharide vaccine covering 23 serotypes developed by Merck, was first approved for use in older adults and the elderly to prevent pneumococcal disease. This vaccine contains capsular polysaccharide from serotypes 1, 2, 3, 4, 5, 6b, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. While Pneumovax 23 has been shown to be effective against IPD in immunocompetent adults [7], it is poorly immunogenic in children less than 2 years old [8].

The first effective pneumococcal vaccine for children less than 2 years old and infants was developed based on the success of the *Haemophilus influenzae* type b conjugate vaccine, which elicits an enhanced immune response when the polysaccharide is conjugated to a carrier protein. Prevnar®, a 7-valent pneumococcal conjugate vaccine (PCV), contains the capsular antigens from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to cross reactive material 197 ($CRM_{197}$, a non-toxic diphtheria toxoid protein). Developed by Wyeth (now Pfizer), Prevnar was first approved

and introduced in the US and Canada for use in infants and young children in the year 2000. Within eight years, overall and serotype-specific IPD in Canada were reduced by 48% and 87.5%, respectively [9].

However, given the limited coverage offered by Prevnar, and the increasing burden of disease caused by newly emergent non-vaccine ('replacement') serotypes after Prevnar introduction, two second-generation PCVs, Synflorix®(GlaxoSmithKline [GSK] Biologicals) and Prevnar 13® (Wyeth, now Pfizer) were subsequently developed and approved for infants and young children, both expanding on Prevnar's 7 serotypes to offer protection against 10 and 13 serotypes, respectively. By adding serotypes 1, 5, and 7F in the case of Synflorix, and serotypes 1, 3, 5, 6A, 7F, and 19A in the case of Prevnar 13®, the second-generation PCVs offered additional protection against common disease-causing serotypes in Canada and worldwide. However, not only have these vaccines been less effective than the 7-valent PCV in addressing vaccine-type disease – with roughly 30% of cases of IPD in Canada still due to Prevnar 13® serotypes based on the most recent (2019) National Microbiology Laboratory (NML) data [10], there has been a significant increase in non-vaccine-type IPD since their introduction due to additional replacement serotypes. In Canada, rising incidence of IPD due to serotype 3 (contained in Prevnar 13®) and serotype 22F (a replacement serotype) are of particular concern [11].

In addition to the issues concerning their overall efficacy, the second-generation PCVs, like their predecessor, are relatively complicated and expensive to produce, making them difficult for low-income countries to afford without considerable external financial assistance. Low- and middle-income countries (LMICs) that do not qualify for financial support via Gavi, The Vaccine Alliance (Gavi) can rarely afford these vaccines within their health budgets. An exception is PNEUMOSIL® [12,13], a 10-valent PCV manufactured by the Serum Institute of India, Pvt., Ltd., which achieved World Health Organization (WHO) prequalification (PQ) in December 2019. However, the effectiveness of PNEUMOSIL will also be limited by the increasing burden of disease caused by non-vaccine serotypes. Prevnar 20™ [14], a 20-valent PCV manufactured by Pfizer, and VAXNEUVANCE™ [15], a 15-valent PCV manufactured by Merck, achieved US marketing authorization for adults 18 years of age and older in June 2021 and July 2021, respectively. Prevnar 20™ has been approved for use in adults by Health Canada in May 2022.

### 1.4 Rationale for IVT PCV-25 Development

To address the above-mentioned issues, Inventprise Inc has partnered with PATH (a global health organization based in Seattle, Washington) to develop a safe, effective and low-cost third-generation PCV vaccine that will prevent IPD, pneumonia, and otitis media due to the remaining predominant serotypes causing disease in children, particularly those residing in Africa and other low- and middle-income regions of the world. The resulting candidate vaccine (IVT PCV-25) contains capsular polysaccharides from 25 pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, and 35B. Table 3 provides a comparison of the vaccine serotypes included in IVT PCV-25 to those included in currently licensed PCVs.

**Table 3. Comparison of IVT PCV-25 vaccine serotypes with vaccine serotypes included in currently licensed PCVs**

| Vaccine | Vaccine Serotypes |
|---|---|
| IVT PCV-25 | 1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, 35B |
| Prevnar 20™ [14] | 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F 22F, 23F, 33F |
| VAXNEUVANCE [15] | 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F |
| Prevnar 13® [16] | 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F |
| Synflorix [17] | 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F |
| PNEUMOSIL [12,13] | 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F |

The selection of the serotypes contained in IVT PCV-25 was based on their longstanding or recently identified status as the most common invasive serotypes globally. Capsular polysaccharides from the serotypes in Prevnar 13® and Prevnar 20™ were included due to their established global importance as invasive serotypes. Serotype 6C has been included in preference to 6A since serotype 6B provides some partial cross-protection against serotype 6A [18]. Additional capsular polysaccharides from the serotypes 2 [19,20] , 6C [14], 9N [21], 15A [22], 16F [23], 24F [24], 35B [25] were included in the IVT PCV-25 vaccine due to their global importance and potential for invasiveness (Table 4).

**Table 4. Rationale for Selection of Vaccine Serotypes Contained in IVT PCV-25**

| Serotypes | Rationale for Inclusion |
|---|---|
| 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F | Serotypes most likely to cause IPD globally and included in Prevnar 13® [16] |
| 22F, 33F | Serotypes known to be invasive and included in Prevnar 20® and VAXNEUVANCE [14,15] |
| 6C | Due to demonstrated cross-protection between serotype 6A and 6B (both included in Prevnar 13®), serotype 6C is substituted for serotype 6A. Serotype 6C is an increasing cause of invasive, antimicrobial-resistant pneumococcal disease [18]. |
| 2 | A highly invasive serotype recently associated with IPD in several LMICs, specifically Bangladesh, Guatemala, and Israel [19,20]. |
| 8 | Cause of IPD in children <5 years of age in post-2010 era in non-Gavi and Gavi countries |
| 9N | Invasive serotype in children <5 years of age for which there is no demonstrated cross-protection by serotype 9V in the currently licensed PCVs [21] |
| 10A | One of the most common invasive serotypes in pediatric and adult populations in both high-income countries as well as LMICs |
| 12F | A highly invasive serotype known to cause epidemic disease |
| 15A, 15B | Serotypes found as a common cause of IPD in children <5 years of age, especially in non-Gavi countries, associated with significant antimicrobial resistance |

| Serotypes | Rationale for Inclusion |
|---|---|
| 16F | Increasing cause of IPD in children <5 years of age, in Gavi and non-Gavi countries [23] |
| 24F | Emerging invasive serotype recently described as the most common cause of meningitis in France, as well as reports from Argentina, Germany, Peru and Papua New Guinea [24] |
| 35B | Emerging invasive serotype, associated with multi-drug resistance [25] |

$CRM_{197}$ conjugate vaccines involve the joining of a polysaccharide moiety from bacterial pathogens such as *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Salmonella typhi,* and S*treptococcus pneumoniae* to $CRM_{197}$, a non-toxic mutant of diphtheria toxin. $CRM_{197}$ is isolated from *Corynebacterium diphtheriae* and differs from wild-type diphtheria toxin, in that a point mutation at amino acid position 52 substitutes glycine with glutamic acid, which eliminates enzymatic activity and toxicity [26]. $CRM_{197}$ conjugate vaccines have been demonstrated to be safe and well tolerated and to induce immunologic memory, boostability and herd protection. The co-administration of multiple vaccines based on the same protein carrier requires careful evaluation due to potential interactions and consequent impact on immune responses to the antigen. Co-administration of $CRM_{197}$ conjugate vaccines may interfere with immunogenicity through antigen competition and carrier-induced epitope suppression inducing either positive or negative effects on antibody responses that vary greatly between vaccines [27-29].

Finally, Inventprise Inc. has committed to make IVT PCV-25 available and accessible at an affordable price to LMICs. This same vaccine will also be made available in high income regions.

### 1.5 Summary of safety profile of hydrazine and PEG in humans

An important reason that Inventprise has selected the HZ-PEG-HZ linker is the positive safety profile of hydrazine which has previously been used for conjugation in the meningococcal conjugate vaccine MenAfriVac®, of which more than 300 million doses have been administered without any safety concerns.

Additionally, PEG used as a conjugate or added as an excipient has been approved for use in numerous drugs, biologicals, and in the mRNA vaccine including in children.

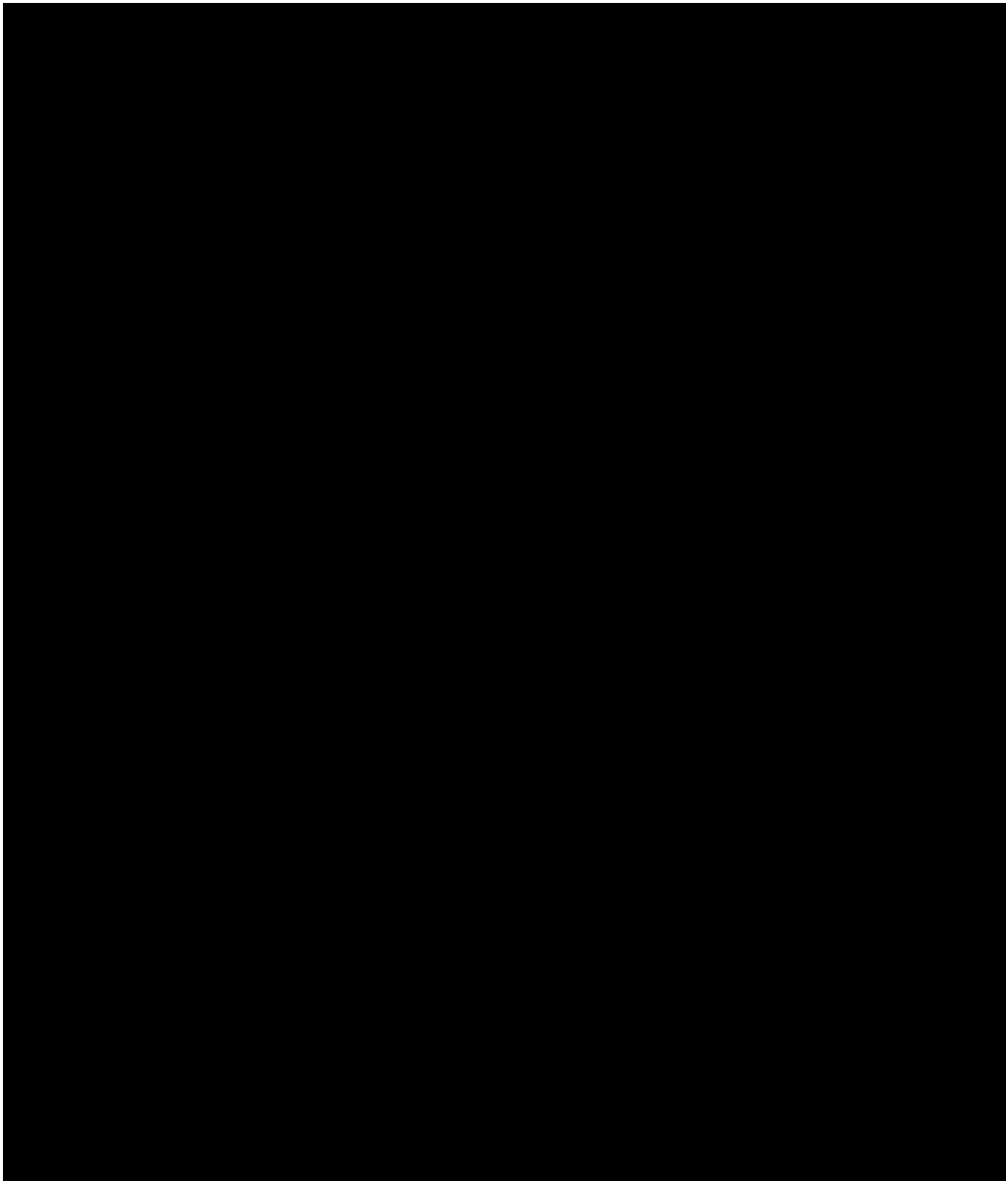
There have been numerous reports of immediate hypersensitivity reactions in humans exposed to drugs, biologicals, and vaccines containing PEG added either as an excipient to the product or as a conjugate to the active drug moiety [30-34]. Although considered rare, such hypersensitivity reactions can require prompt medical intervention and in some cases hospitalization. These rare adverse events (AEs) rare have been associated with IgM, IgG, and IgE antibodies to PEG although the presence of anti-PEG antibodies are not predictive of the probability of developing immediate-type hypersensitivity-type reactions.

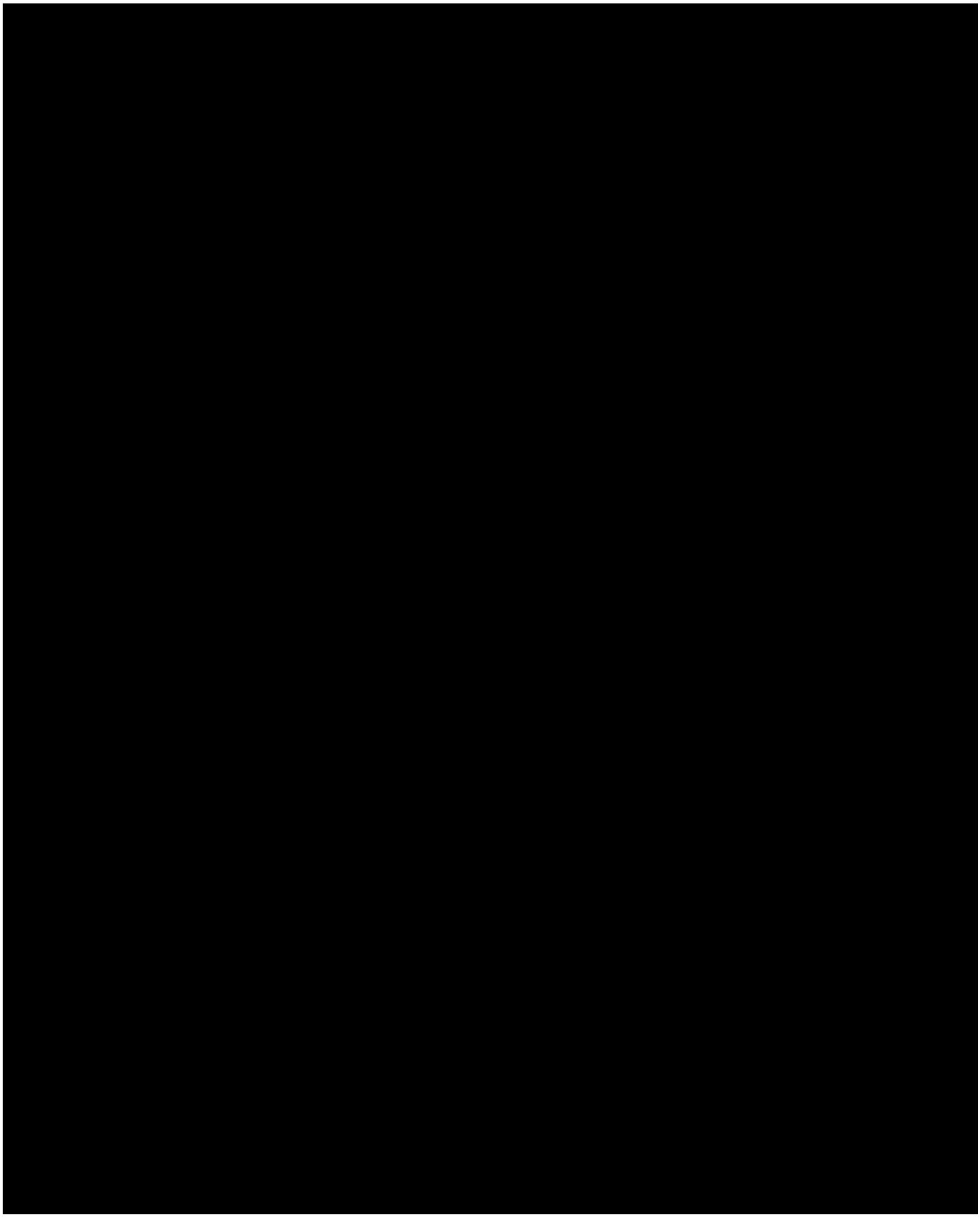
In a retrospective study of the long-term safety of PEG-containing therapies in the pediatric population, children weighing 10 kg who were exposed to as much as 2.7 grams of PEG per year (in pegylated Factor VIII), and children weighing 50 kg exposed to as much as 21.8 gr per year were not found to be adversely affected [34]. These quantities of annual PEG exposure are substantially higher than the microgram levels of PEG that will be given in IVT PCV-25.

### 1.6 Summary of Preclinical Studies

A series of preclinical studies have been conducted to evaluate the immunogenicity and safety of IVT PCV-25, and to support the formulation of IVT PCV-25 vaccine candidate evaluated in this Phase 1/2 clinical study. A brief overview of these studies is provided in Table 5 below. Refer to the Investigator's Brochure for additional details.

**Table 5. Preclinical studies conducted to evaluate IVT PCV-25**





[redacted]

[redacted]

### 1.7 Summary of First-in-Human Clinical Study (NCT05540028)

The Phase 1/2 age de-escalation study (NCT05540028) was initiated in 2022 in adults, 18-40 years of age. The adult cohort of 60 adult participants were randomized 1:1 to receive either a single dose of IVT PCV-25 vaccine or the comparator vaccine, Prevnar 20™ by intramuscular injection. The Data and Safety Monitoring Board (DSMB) reviewed the cumulative unblinded safety data through day 28 after vaccination in all 60 adult participants and concluded that the reactogenicity and safety of the investigational product was favorable and approved the original protocol to proceed as planned. A summary of the blinded group level solicited local and systemic AEs through day 7 after vaccination is shown in Table 6.

**Table 6. Solicited AEs by Severity**

| Solicited AE | n (%), E | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) |
|---|---|---|---|---|---|
| Local Solicited AE* | **54 (90.0%), 59** | **33 (55.0%)** | **21 (35.0%)** | **0 (0.0%)** | **0 (0.0%)** |
| Injection site pain and/or tenderness | 54 (90.0%) | 34 (56.7%) | 20 (33.3%) | 0 (0.0%) | 0 (0.0%) |
| Injection site redness | 3 (5.0%) | 1 (1.7%) | 2 (3.3%) | 0 (0.0%) | 0 (0.0%) |
| Injection site swelling | 2 (3.3%) | 1 (1.7%) | 1 (1.7%) | 0 (0.0%) | 0 (0.0%) |
| | | | | | |
| Systemic Solicited AE* | **43 (71.7%), 86** | **22 (36.7%)** | **18 (30.0%)** | **3 (5.0%)** | **0 (0.0%)** |
| Headache | 27 (45.0%) | 18 (30.0%) | 7 (11.7%) | 2 (3.3%) | 0 (0.0%) |
| Fatigue | 24 (40.0%) | 12 (20.0%) | 9 (15.0%) | 3 (5.0%) | 0 (0.0%) |
| Myalgia | 17 (28.3%) | 12 (5.0%) | 4 (6.7%) | 1 (1.7%) | 0 (0.0%) |

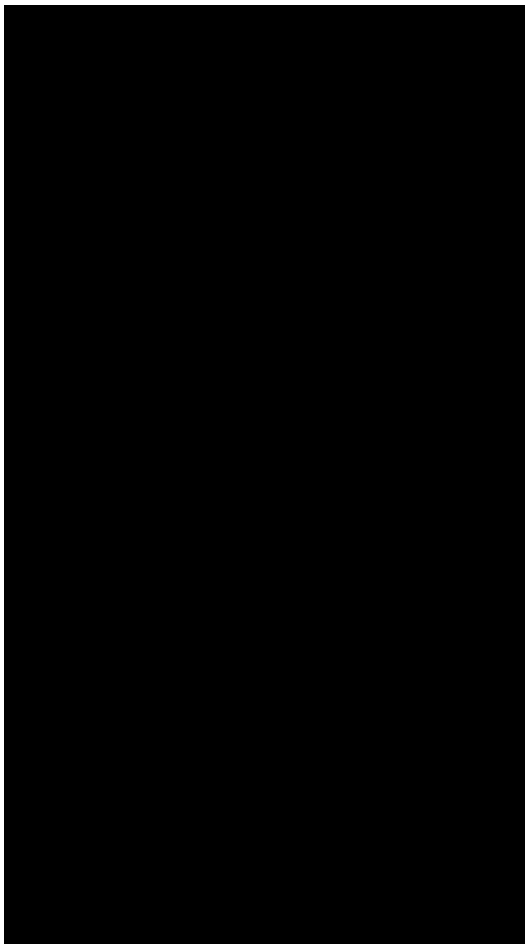
n: number of subjects with event; E: number of events;

*: the three most frequently reported solicited AEs

A total of 49 unsolicited AEs were reported through Day 29, of which 3 AEs were classified as related to investigational product. The three most frequently reported AEs were Headache, n=7 (11.7%), Nasopharyngitis, n=5 (8.3%), and COVID-19, n=4 (6.7%). Up through Day 29, there were no serious adverse events (SAEs) reported. Additional safety information can be found in the Investigator Brochure.

The Sponsor, consultants, and PATH reviewed the unblinded serotype-specific IgG antibody concentrations at baseline and 28 days after vaccination from the adult participants after the first 26 participants completed Visit 3, and also from the entire 60-person cohort. The immunogenicity as represented by the geometric mean ratio (GMR) of the IgG concentrations at 28 days post vaccination in participants vaccinated with IVT PCV-25 compared to participants vaccinated with Prevnar 20™ are shown in Table 7. The blue-shaded serotypes are shared between IVT PCV-25 and Prevnar 20™. The green-shaded serotypes are those unique to IVT-PCV-25. The red-shaded serotype 6A is unique to Prevnar 20™. There was decreased GMRs in 14 of the 18 commonly shared serotypes between IVT PCV-25 and Prevnar 20™ although the sample size was too small to make any statistical significance with precision due to the descriptive study design.

**Table 7. Geometric mean ratio of GMCs 28 days after vaccination.**



[redacted]

[redacted]

### 1.8 Study Rationale

[redacted]

Inventprise Inc. now (subject of this protocol) intends to conduct an adult only study with various dose-ranging formulations to obtain safety and reactogenicity and also supportive immunogenicity data to enable age de-escalation of one or more of these formulations directly to a phase 2 infant study without prior age de-escalation to toddlers. Inventprise, Inc. has manufactured a new lot of IVT PCV-25 and reformulated the product into three different antigen and adjuvant combinations to be tested in the Phase 2 trial. Inventprise Inc. is evaluating the new formulations in a toxicology study and will be included in an updated Investigator Brochure before advancement to infants.

It is important to note that the magnitude of the type of protective immune responses elicited in adults (serotype-specific OPA antibodies) versus infants are not necessarily predictive of the protective immune responses elicited in infants (serotype-specific IgG concentrations), and that the regulatory criteria for approval of a PCV indication differ between adults and infants. Therefore dose-ranging in both adults and infants are necessary to optimize final dose selection for pivotal Phase 3 studies in infants and in adults. Furthermore, antigenic competition due to the large number

of serotypes included in a candidate vaccine have been shown to reduce both functional OPA and serotype-specific IgG concentrations, warranting an evaluation of an increased polysaccharide dose for each serotype included in the candidate vaccine and/or increased adjuvant dose. Therefore, three dose formulations have been selected to evaluate whether increasing antigen and/or adjuvant dose elicits comparable immune responses to the gold-standard comparator vaccine, Prevnar 20™.

Final dose selection for Phase 2 and Phase 3 studies may also include a "hybrid" vaccine group that includes an increased polysaccharide dose concentration for one or more serotypes.

The Phase 2 dose-ranging study (CVIA 105) of IVT PCV-25 is designed to provide the necessary assurances of safety, tolerability, and immunogenicity after a single intramuscular administration of IVT PCV-25 in adults. The sample sizes for the 3 adult formulations were weighted toward the highest antigen and adjuvant dosage combination [redacted] in order to provide a reasonable margin of safety to proceed directly to a Phase 2 trial in infants. All analyses of safety/tolerability (primary) and immunogenicity (secondary) data will be descriptive, with the latter including serotype-specific IgG responses and functional antibody responses as measured by OPA. Antibody responses will be measured against the 25 serotypes contained in IVT PCV-25 well as against serotype 6A in order to measure the cross-reactive response due to the presence of serotype 6B in the candidate vaccine.

The first analysis (Interim analysis), that will function as the primary analysis, will be conducted to provide the Sponsor an early look at the safety and reactogenicity data from all 220 adult subjects up through day 28 post-vaccination in order to plan and proceed expeditiously to a Phase 2 trial in infants. This analysis will also include the serotype-specific IgG immune responses (baseline and Day 29 serum samples) from approximately 50% or more of the participants in order to inform how the immune responses from each of the 3 IVT PCV-25 formulations compare to the comparator vaccine. A second analysis that includes individual participant ID-masked OPA results and unblinded group-level OPA summary results from all participants through 28-day post-vaccination will be provided as the data becomes available. [redacted]

## 2. HYPOTHESIS, OBJECTIVES, ENDPOINTS, ESTIMANDS

### 2.1 Study Hypothesis

IVT PCV-25 will have an acceptable safety and tolerability profile in adults.

IVT PCV-25 will be immunogenic and will elicit seroresponses to the serotypes present in the candidate vaccine.

### 2.2 Study Objectives, Endpoints, and Estimands

| OBJECTIVES | ENDPOINTS | ESTIMANDS |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| 1. To describe the reactogenicity, tolerability, and safety of IVT PCV-25 administered as a single-dose regimen to healthy pneumococcal vaccine-naïve adults. | 1. Local reactions (redness, swelling, and pain at the injection site)<br>2. Systemic events (fever, headache, fatigue, muscle pain, joint pain, and rash)<br>3. Unsolicited Adverse events (AEs)<br>4. Serious adverse events (SAEs) | **Population**: Healthy pneumococcal vaccine-naïve adult participants receiving study vaccines<br>**Population-level summary:**<br>1. Number and severity of solicited local reactions within 7 days after vaccination (redness, swelling, and pain at the injection site) by group<br>2. Number and severity of solicited systemic AEs within 7 days after vaccination by group<br>3. Number and severity of unsolicited AEs within 28 days after vaccination by group<br>4. Number of SAEs within 6 months after vaccination by group |
| **Secondary:** | **Secondary :** | **Secondary:** |
| 1. To describe the immune responses elicited by a single dose of IVT PCV-25 against the 25 serotypes contained in IVT PCV-25 (1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, 35B) as well as serotype 6A, alone and in comparison to the antibody responses | 1. Serotype-specific immunoglobulin G (IgG) antibody responses<br>2. Serotype-specific functional antibody responses measured by Opsonophagocytic Assay (OPA) | **Population:** Healthy pneumococcal vaccine-naïve adult participants receiving study vaccines, complying with the key protocol criteria, and providing evaluable sample at baseline and 28 days after vaccination<br>**Population-level summary:**<br>1. Geometric mean concentrations (GMC) of serotype-specific IgG at each time point (Day 1 and Day 29) by group |

| | | |
|---|---|---|
| against these serotypes induced by Prevnar 20™ in healthy adults | | 2. Geometric mean fold rise (GMFR) in serotype-specific IgG GMCs from baseline to Day 29 after vaccination by group<br>3. Percentage of participants achieving a ≥4-fold IgG rise from baseline to Day 29 after vaccination by group<br>4. Ratio of GMCs between IVT PCV-25 and Prevnar 20 groups 28 days after vaccination<br>5. Ratio of IgG GMFR between IVT PCV-25 and Prevnar 20 groups<br>6. Geometric mean titers (GMTs) of serotype-specific OPA antibodies at each time point (Day 1 and Day 29) by group<br>7. Geometric mean fold rise (GMFRs) in serotype-specific OPA GMTs from baseline to Day 29 after vaccination by group<br>8. Ratio of GMTs between IVT PCV-25 and Prevnar 20 groups 28 days after vaccination<br>9. Ratio of OPA GMFR between IVT PCV-25 and Prevnar 20 groups |

## 3. STUDY DESIGN

In this prospective, multicenter, randomized, active-controlled, observer-blind Phase 2 study, 220 adult (age 18-49 years) eligible participants will be randomized to four groups as shown below (Table 8). The four groups will be conducted concurrently and randomized in a 2:3:4:2 ratio.

**Table 8. Randomization Scheme**

| Group | n | [redacted] | | |
|---|---|---|---|---|
| Group A | 40 | | | |
| Group B | 60 | | | |
| Group C | 80 | | | |
| Group D | 40 | Prevnar 20™ comparator | | |
| [redacted] | | | | |

For all participants, eligibility to participate in the study, including assessment of medical history, vital signs and physical examination, will be undertaken after the participant signs the informed consent form (ICF).

Each adult will undergo a total of 4 clinic visits (V), including at least one screening visit (V0) not more than 28 days prior to Day 1 (V1), a vaccination visit on Day 1 (V1), follow-up clinic visits at 7 (+3) and 28 (+7) days post-vaccination (V2 and V3, respectively) as shown in Table 9. Daily local and systemic reactogenicity will be monitored during the 7 days after vaccination (Day 1 and following 6 days) by memory aid. Blood will be collected for hematological and biochemical laboratory tests at screening (V0) and Day 8 (V2). Blood will be collected at baseline (V1) and 28 days post-vaccination (V3) to assess serotype-specific IgG antibody and OPA functional antibody responses in all participants. There will be a final follow-up call on Day 169 (V4) .

**Table 9. Study Schedule**

| Groups | Visits/Study Day | | | | |
|---|---|---|---|---|---|
| | **Screening** | **V1 (D1)** | **V2 (D8)** | **V3 (D29)** | **V4 (D169)** |
| | -28 to 0 | 1 | V1+7 (+3) | V1+28 (+7) | V1+168 (+14) |
| IVT PCV-25 Group A | B* | B, X | B* | B | — |
| IVT PCV-25 Group B | B* | B, X | B* | B | — |
| IVT PCV-25 Group C | B* | B, X | B* | B | — |
| Prevnar 20™ Group D | B* | B, X | B* | B | — |

B = blood draw (serum); X = study vaccination

*Blood draw for clinical laboratory tests

An independent DSMB will review unblinded safety data after the last participant completes the 28-day follow-up visit (V3) in order to plan for advancement to the infant study.

The sample sizes for each group were selected and weighted toward the higher antigen and adjuvant dose combinations to ensure that the safety assessment in each group at the interim analysis was adequate to advance to an infant Phase 2 trial and would reflect the probability for similar dose ranges to be included in a study in infants.

The first study (interim) report will include the safety data up through Day 29 from the complete 220 adult cohort (DSMB review) and the interim serotype-specific IgG results of IVT PCV-25 from approximately 50% or more of the participants in study. The Sponsor plans to submit the report for a follow-on dose-ranging Phase 2 trial in infants, aged 8-11 weeks at first dose. A second analysis will include the OPA results through Day 29 from the complete 220 adult cohort as they become available.

The Sponsor and its consultants, PATH, representatives from the Bill & Melinda Gates Foundation, and the site Investigators will review the group-level, unblinded interim safety report in order to prepare for a dose-ranging Phase 2 trial in infants.

The Sponsor and its consultants, PATH, and representatives from the Bill & Melinda Gates Foundation will review the unblinded group-level and individual level (with participant ID masked) serotype-specific IgG antibody responses from the first analysis and the unblinded group-level and individual level (with participant ID masked) serotype-specific OPA results at baseline and Day 29 from the second analysis as they become available to ensure that the immune responses to IVT PCV-25 are sufficient to proceed to a dose-ranging Phase 2 trial in infants. The site investigators will be provided the group-level immunogenicity results but will remain blinded to the individual serotype-specific IgG and OPA results until study end.

The third and final study report will include the complete safety data up through Day 169 from all participants with the complete IgG and OPA immunogenicity results from all the participants.

After informed consent is obtained, participants will be screened to determine eligibility. Randomization will take place only after a participant has satisfied all eligibility criteria, including confirmation of having no acute illness or abnormal vital sign that precludes vaccination.

Each participant will undergo a total of 4 clinic visits (V), including at least one screening visit (V0) not more than 28 days prior to Day 1 (V1), a vaccination visit on Day 1 (V1), and follow-up clinic visits at 7 (+3) and 28 (+7) days post-vaccination (V2 and V3, respectively). Re-screening is permissible if the window period exceeds 28 days.

Blood will be collected for hematological and biochemical laboratory tests at screening (V0) and Day 8 (V2). Blood will be collected at baseline (V1) and 28 days post-vaccination (V3) to assess

serotype-specific IgG antibody responses and to assess serotype-specific functional responses as measured by OPA. There will be a final follow-up call at Day 169 (V4) to obtain any safety information (SAEs) that may have occurred since Visit 3. The study schema for the adult cohort is presented in Table 9.

The DSMB will review unblinded safety and reactogenicity data from all adult participants after the last participant in the adult cohort completes the 28-day follow-up visit (V3).

# 4. STUDY POPULATION

## 4.1 Description of Study Population

The study population will consist of healthy male and female pneumococcal vaccine-naive adults from 18 through 49 years of age, recruited and screened by the site staff at the participating study sites in Canada. Participants will by recruited to participate in the study from within the Canadian Immunization Research Network and possibly other clinical trial sites in Canada. In order to be eligible for randomization and vaccination, prospective participants must meet all of the inclusion criteria and none of the exclusion criteria.

## 4.2 Inclusion Criteria

Participants will be eligible for randomization if all of the following inclusion criteria apply at the time of screening:

1. Healthy adults who are 18 through 49 years old on the day of randomization (Day 1).

   Note: 'Healthy' status is to be determined by medical history, physical examination, and clinical judgment.

2. Participant must provide voluntary written informed consent to participate in the study.
3. Participant must be able to comprehend and comply with study requirements and procedures and be willing and able to return for all scheduled follow-up visits.
4. Adult female participants who are not surgically sterile must have a negative pregnancy test at screening and negative pregnancy test prior to vaccination. They will be advised through the informed consent process to avoid becoming pregnant through Day 57 of the study and must agree to employ a highly effective form of birth control through Day 57 of the study.

   Note: Highly effective forms of birth control are the following: credible history of continuous abstinence from heterosexual activity, hormonal contraceptives (oral, injectable, implant, patch, and ring), double barrier contraceptives (condom and cervical cap or diaphragm, either with spermicide) and intrauterine device. When using contraceptives, participants must have been using their current contraceptive for the past 2 months to be eligible. Adult female participants with documented sterilization via tubal ligation or hysterectomy may be enrolled and not be participant to pregnancy testing.

### 4.3 Exclusion Criteria

An adult who meets any of the following exclusion criteria at screening will not be eligible for randomization in the study:

1. Use of any investigational medicinal product within 90 days prior to randomization or planned use of such a product during the period of study participation.
2. Adults who have previously been vaccinated against *S. pneumoniae*.
3. History of microbiologically confirmed invasive disease caused by *S. pneumoniae*.
4. History of allergic disease (including angioedema) or history of a serious reaction to any prior vaccination or known hypersensitivity to any component of the study vaccines, including PEG.
5. Any abnormal vital sign deemed clinically relevant by the PI.
6. Acute illness at time of randomization (moderate or severe) and/or fever (body temperature of ≥ 38.0°C) see note below.
    a. Note: A minimum of 48 hours following a documented fever must pass before the participant can be vaccinated.
7. History of any non-study vaccine administration within 14 days of study vaccine administration.
8. No planned vaccines until after Day 29 (Visit 3).
9. Chronic administration (defined as more than 14 consecutive days) of immunosuppressant or other immune modifying drugs prior to the administration of the study vaccine (and within the 6 months prior to administration of the study vaccine), including the use of glucocorticoids. The use of topical and inhaled glucocorticoids will be permitted.
10. Administration of immunoglobulins and/or any blood products within the 6 months prior to administration of the study vaccine or anticipation of such administration during the study period.
11. Any medical or social condition that in the opinion of the PI*, may interfere with the study objectives, pose a risk to the participant, or prevent the participant from completing the study follow-up.
12. Any screening laboratory test result outside the normal range and with toxicity score ≥ 2, unless allowed by the PI, IVT Chief Medical Officer (CMO), and PATH Medical Officer (MO). A participant may repeat each laboratory assessment once during the screening period, with the most recent laboratory value being used for evaluation of exclusion criteria.
13. A positive serologic test for human immunodeficiency virus (HIV)-1 or HIV-2 (HIV 1/2 Ab), hepatitis B (HBsAg) or hepatitis C (HCV Ab).

* The term "PI" is used throughout this protocol to refer to either the PI or designee.

14. History of malignancy, excluding non-melanoma skin and cervical carcinoma in situ.
15. Recent history (within the past year) or signs of alcohol or substance abuse.
16. History of major psychiatric disorder.
17. Female adult participants who are pregnant or breastfeeding.
18. Participant is an employee of, or direct descendant (child or grandchild) of any person employed by the Sponsor, PATH, the Contract Research Organization (CRO), the PI.

# 5. STUDY PRODUCTS

## 5.1 IVT PCV-25

### 5.1.1 Product Description

The 3 doses of IVT PCV-25 selected for the Phase 2 trial [redacted]

Formulation A: [redacted]

Formulation B; 2.2/250: [redacted]

Formulation C; 4.4/250: [redacted]

### 5.1.2 Manufacturer

IVT PCV-25 is manufactured and supplied by Inventprise, Inc.

### 5.1.3 Presentation and Formulation

IVT PCV-25 will be supplied in a five-dose vial, in cartons containing 10 labeled vials. Each vial label will include the following information in both English and French: name of the medicinal product, strength, dose and dose volume, route of administration, lot number, retest dates, storage

condition, a cautionary statement ("For Human Clinical Trial Use Only"), and the Sponsor's name and address.

### 5.1.4 Storage

IVT PCV-25 should be stored between 2°C and 8°C. It must not be frozen.

### 5.1.5 Potential Safety Risks

As with any vaccine, severe allergic reaction is a potential rare event. Known hypersensitivity to any component of the vaccine (including diphtheria toxoid, $CRM_{197}$, and PEG) is a contraindication to vaccination.

## 5.2 Prevnar 20™

### 5.2.1 Product Description

Prevnar 20™ is approved for use in adults in Canada. A single 0.5 mL dose of Prevnar 20™ contains approximately 2.2 µg of each of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F saccharides, 4.4 µg of 6B saccharides, all conjugated to CRM197 and adsorbed onto aluminum phosphate (0.125 mg aluminum). The vaccine is a turbid white suspension.

### 5.2.2 Manufacturer

Prevnar 20™ is manufactured by Wyeth Pharmaceuticals, a subsidiary of Pfizer.

### 5.2.3 Presentation and Formulation

Prevnar 20™ is supplied in a single dose 0.5 mL glass pre-filled syringe (PFS**)** with a plunger stopper and protective tip cap. It will be labeled with the following minimum information: name of the medicinal product, route of administration, expiry date, lot number, and dose volume.

### 5.2.4 Storage

Prevnar 20™ should be stored between 2°C and 8°C. It must not be frozen.

### 5.2.5 Potential Safety Risks

Hypersensitivity to any component of the vaccine (including diphtheria toxoid and $CRM_{197}$) is a contraindication. For Prevnar 20™, in adults 18 years of age and older, the most commonly reported solicited adverse reactions (>10%) were pain at the injection site, muscle pain, fatigue, headache, and arthralgia. Additionally, injection site swelling was also reported (>10%) in adults 18 through 59 years of age.

### 5.3 Vaccine Storage, Transport, and Temperature Monitoring

The temperature of study vaccines will be monitored during shipment and storage at the sites to ensure that temperature deviations do not occur.

The temperature of all vaccine shipments will be monitored throughout transit using a continuous temperature monitoring system. Vaccines will not be used until the temperature of the vaccines throughout transit has been confirmed to be within acceptable limits.

Upon receipt at the site, all vaccines will be stored at 2°C to 8°C in dedicated refrigerators that are locked, and not accessible to unauthorized personnel. The refrigerators will be under continuous temperature monitoring with maintenance of daily temperature logs and connected to a power source with a reliable back-up system.

It is the responsibility of designated unblinded site personnel to ensure that vaccine has not been exposed to temperatures outside the allowed range during transport or storage at the facility prior to being dispensed for vaccination. Should there be a deviation outside the allowed temperature range, the affected vaccine(s) will be quarantined. The temperature deviation will be reported to PATH and IVT, Inc. who will advise the unblinded study staff of the action to be taken based on the magnitude and duration of the temperature deviation. All vaccine accountability procedures, including cold chain monitoring will be documented and are the responsibility of the unblinded study personnel.

### 5.4 Dose Preparation and Administration

Appropriately trained, unblinded study personnel will be responsible for preparing study vaccine doses in accordance with the randomly determined assignment, administering the study vaccines, and handling all vaccine accountability procedures. Unblinded personnel will not participate in the other aspects of the clinical trial after vaccine administration, to help ensure the integrity of the blind at the site. The unblinded personnel will not reveal participants' randomization assignments to the participants, or staff associated with the Sponsor, PATH, CRO, or site. Unblinded personnel will retrieve a participant's randomization assignment after being informed by the PI that a participant is eligible for randomization. They will prepare the study vaccine based on the participant's randomization assignment in a setting distinct from the study staff, and then the unblinded study nurse will administer study vaccine to a participant. All study personnel will be trained in immediate management of AEs following immunization including anaphylaxis. Vaccination will take place in a clinical setting in which there is immediate access to the medical personnel, equipment, and medications required for emergency resuscitation.

Since IVT PCV-25 and Prevnar 20$^{TM}$ are suspensions containing an alum adjuvant, study vaccine must be shaken gently immediately prior to use, in order to obtain a uniform homogenous white suspension. Inspection of each vial/PFS will occur immediately prior to use. If a vial/PFS or its contents appear unusual in any way, the vial/PFS will not be used, and procedures detailed in the Pharmacy Manual and Lab Manual for documentation and disposal will be followed. One separate

multi-dose single vial will be used for each participant randomized to be vaccinated with IVT PCV-25.

A detailed account of procedures related to preparation and administration of study vaccine will be included in the Pharmacy Manual .

- IVT PCV-25 or Prevnar 20™ will be administered to adults as an intramuscular injection into the mid-deltoid muscle of the participant's non-dominant arm.

Injectable vaccines may be given at other sites if there is a good reason to do so (e.g., local infection, or pre-existing swelling).

### 5.5 Accountability and Disposal

Following vaccination, the single multi-dose vaccine vial/PFS will be labeled with the participant ID of the participant to whom the vaccine has been administered using prepared stickers. The person who administered the vaccine and the time and date of vaccine administration will also be documented in an appropriate vaccine accountability log on the day of vaccination. All used vials/PFS without the needle will be stored in a dedicated space that is accessible only to the unblinded site personnel and the unblinded CRO monitor (and ultimately disposed of after completion of the study).

In case a vial/PFS of vaccine is broken or unusable, the unblinded site personnel will promptly inform the unblinded monitor and store the vial/PFS for accountability, following all safety precautions. In case a broken vial/PFS cannot be stored safely for accountability, appropriate discard and documentation will be followed after consultation with the unblinded monitor. Study product prepared but not administered to participants, and all unused study product, will likewise be documented per drug accountability processes and discarded after the study is completed or terminated after notification by the CRO unblinded monitor.

The designated unblinded site personnel will maintain a complete and accurate inventory of study vaccines received (including the quantity of vaccines received, date of receipt, condition at receipt, temperature noted during transit), those administered, and any broken or destroyed.

The unblinded CRO monitor will visit the sites periodically throughout the trial to review and verify vaccine accountability records, as well as to ensure compliance with all trial procedures by the unblinded site personnel. After final vaccine accountability is completed by the unblinded CRO monitor, any used or unused vials/PFS of study vaccine will be destroyed at the site under the supervision of the unblinded site personnel.

# 6. STUDY PROCEDURES

## 6.1 Recruitment

Prospective participants will be recruited by study sites by means of 1) print and/or electronic media prompting calls by interested individuals to the site, 2) contacting individuals who have previously given permission to be contacted about future research studies, and 3) word of mouth. All recruitment materials will be approved by the center's Ethics Committee (EC) /Research Ethics Board (REB) prior to use. During recruitment telephone calls, prospective participants will be given information (e.g., some elements of inclusion and exclusion criteria) to help them decide whether to make an appointment to learn more about the study, and, if interested to take part in the informed consent process.

### 6.1.1 Initial and Continuing Informed Consent

Informed consent is the process of ensuring that study participants fully understand the purpose of the study, procedures, and benefits and risks. The informed consent process continues throughout the study. Key study concepts will be reviewed with the participant at designated times and as needed; this review process will be fully documented. Additionally, if any new information becomes available that, in the judgment of the Sponsor and/or the PI may affect participants' decision to continue in the trial, such information will be shared, and may be the basis for requiring a new consent form to be signed.

The Standard Operating Procedure (SOP) for informed consent will be followed at each study site. The participant will review the consent form and have adequate opportunity to discuss the study with an investigator or a qualified designee. The consent process will be documented in the participant's source documents and must comply with the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) Good Clinical Practice (GCP) guidelines and any local regulatory requirements.

The consent form will be signed and dated by the person conducting the consent process, the participant, and investigator (if applicable per local requirements). A copy of the signed ICF will be provided to the participant and the original ICF will be filed with other participant records by the study staff.

The ICF will only be completed once at the time of enrollment and prior to screening (unless new information necessitating repeat consent is required).

Regardless of duration on study, ongoing willingness of participation will be documented in the source documents at each visit.

## 6.2 Study Visits

General information:

- Study-specific procedures for participants are indicated in Appendix 1.

- Blood sample volumes at designated visits are detailed in Section 7.
- Participants will be reminded at each visit to contact the study staff to report any SAE occurring at any time during the study.
- Participant ID will be confirmed on day of each visit
- Scheduling of subsequent visits will occur at each visit.

### 6.2.1 Screening

Once informed consent has been documented, the participant will be considered to be enrolled in the trial and may be screened to determine study eligibility. All inclusion/exclusion criteria must be assessed from data obtained within the screening period, unless otherwise specified in the eligibility criteria. After informed consent has been obtained, screening procedures will be performed.

The PI will use good clinical judgment in considering a prospective participant's overall eligibility. Individuals who are not deemed eligible will be recorded as screen failures, along with the basis for this determination, on the appropriate CRF. Individuals who screen fail may not be rescreened.

At screening, screening positive serum or urine pregnancy tests and laboratory test results outside the normal range and with toxicity score ≥ 2 are exclusionary unless allowed by the PI, IVT Chief Medical Officer (CMO), and PATH Medical Officer (MO) (see Appendix 4). During the defined screening period for adults, prospective participants may return once for repeat assessments to be reassessed for eligibility. The last measurement will be taken as the baseline for purposes of analysis.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

### 6.2.2 Randomization and Vaccination Visit General Information

1. Eligibility for vaccination will be confirmed based on review of inclusion/exclusion criteria. Any participant who cannot be vaccinated due to an acute abnormality (e.g., ≥ Grade 2 acute illness, or abnormal vital sign deemed clinically relevant by the PI) may return once the acute issue has resolved, if deemed appropriate by the PI. A minimum of 48 hours must have passed after a documented fever (body temperature of ≥ 38°C) before a participant can be vaccinated.

2. Pregnancy testing (urine) will be collected from all women of childbearing potential (WOCBP).

3. At Visit 1, all participants will be randomized to a vaccine group if eligibility is confirmed by the investigator(s). The randomization ID will be recorded by unblinded study staff, who will maintain a list documenting the study vaccine assigned and administered to given randomization IDs in a secure location that is not accessible to blinded study staff. The participant will be referred to by a participant ID for the remainder of the study.

4. Approximately 50 mL of blood will be obtained by venipuncture for immunogenicity testing prior to the administration of the study product.
5. After the study product is administered, the participant will be observed by blinded study staff for at least 30 minutes post-vaccination.
6. Vital signs and any solicited AEs will be recorded at 30 (+10) minutes post-vaccination. See Appendices 2 and 3 for relevant severity grading scales.
7. During the observation period, the participant will be provided with a ruler, thermometer, and memory aid, and given instructions on how to complete the memory aid. The participant will be instructed to collect solicited AEs daily for seven days (the day of Visit 1 and the following six days) by recording them in the memory aid, preferably at approximately the same time each day. The participant will also be instructed to record unsolicited AEs and concomitant medications on the memory aid.
8. The participant will be instructed to call the study staff in the event of any severe (Grade 3) symptoms, if there is ongoing local or systemic reactogenicity on Day 8, or for any other health issues that require medical attention. The PI will assess the need to evaluate such events/issues at an unscheduled visit.

### 6.2.3 Visit 2 General Information

1. Unsolicited AEs will be recorded, including assessment of relatedness to vaccination, severity, and outcome. Ongoing unsolicited AEs will be reviewed.
2. The completed memory aid will be reviewed with the participant for completeness and accuracy. Possible inaccuracies will be clearly documented.
3. Blood sample obtained for safety labs.

### 6.2.4 28-Day Post-Vaccination Visit (Visit 3)

1. Unsolicited AEs will be recorded, including assessment of relatedness to vaccination, severity, and outcome. Ongoing unsolicited AEs will be reviewed.
2. The completed memory aid will be reviewed for completeness and accuracy. Possible inaccuracies will be clearly documented.
3. Approximately 50 mL of blood will be obtained by venipuncture for immunogenicity testing.
4. Pregnancy testing (urine) will be collected from all women of childbearing potential (WOCBP).

### 6.2.5 Six Month Post-Last Vaccination Visits (Visit 4)

1. Participant will be contacted by telephone

2. Participant ID will be confirmed.
3. SAEs since the last visit will be recorded, including any concomitant medications taken for the AE. Any ongoing unsolicited AEs will be reviewed.
4. Participants will exit the study after completion of the Study Exit CRF.

### 6.2.6 Interim Contacts and Visits

Interim unscheduled contacts and visits (e.g., unscheduled visits) in between regularly scheduled follow-up visits may occur at any time at the request of the participant or as deemed necessary by the PI. All unscheduled interim contacts and visits will be captured in the participant's study records and on applicable CRFs.

## 6.3 Participant Discontinuation Termination

Participant discontinuation from study procedures prior to completion of the last study visit may occur for any of the following reasons:

- Withdrawal (defined as discontinuation initiated by a participant): Participation in the study is strictly voluntary. Participants have the right to withdraw their consent from study participation at any time and for any reason, without penalty. The participant may also withdraw due to an AE. Non-coercive attempts (e.g., phone calls) will be made to obtain AE data according to the schedule of events if the participant is willing to provide.
- PI-initiated: The PI may, at their discretion, discontinue a participant from the study if it is considered to be in the participant's best interest to do so (e.g., for safety concerns), or if the participant does not comply with the study requirements.
- Lost to follow-up: For participants who fail to attend scheduled visits, study staff are to make at least three attempts to contact the participant prior to considering the participant as lost to follow-up. These attempts should be recorded in the source documents.
- Sponsor-initiated: For example, if the Sponsor is obliged to end the study for administrative or any other reason, such as a recommendation by the DSMB based upon safety review.

Participants who discontinue prior to first administration of study vaccine will be replaced, whereas those withdrawn after first administration of study vaccine will not be replaced.

The reason for and date of participant discontinuation will be recorded in the relevant CRF. Before concluding the reason for the participant's discontinuation from the study, the PI should make every effort to investigate whether an AE may have been related to the participant's discontinuation from the study. For participants considered lost to follow-up, the discontinuation date for the participant to be captured on the Study Exit CRF page is the date of the participant's last completed study visit.

In the event of participant discontinuation from the study, reasonable efforts should be made to conduct the following procedures (unless participant consent to do so has been withdrawn):

- Update participant contact information.

- Review the memory aid if still in use prior to discontinuation.
- Update any AEs that remained ongoing at the time of the participant's last visit prior to discontinuation.
- Collect any new reportable AEs and concomitant medications since the participant's last visit, based on the protocol-defined reporting period at the time of discontinuation.
- Perform a targeted PE to evaluate any newly reported AEs since the participant's last visit.

### 6.4 Concomitant Medications and Treatments

Concomitant medications will be recorded for any AE with onset ≤ 28 days post-vaccination and for any SAEs that occurs throughout the study. Details on concomitant medications to be recorded include the generic and/or trade name, over-the-counter or herbal, indication, dosage, regimen, route of administration, and start and end dates of the medication.

The following concomitant medications are prohibited during the study; however, they must not be withheld by the treating physician if clinically indicated:

- Any investigational drug/vaccine other than the study vaccines
- Pneumococcal vaccine other than the blinded study vaccine
- Planned vaccines (e.g., influenza, etc.)
- Chronic administration (defined as more than 14 days) of immunosuppressant or other immune modifying agents. For corticosteroids, this means prednisone or equivalent >10 mg per day; topical and inhaled steroids are allowed.
- Administration of immunoglobulins or any blood products during the study period

Use of any prohibited medication must be recorded in the CRF. Whether a participant who uses a prohibited medication will be included in the per protocol (PP) population will be evaluated on a case-by-case basis.

### 6.5 Emergency Unblinding Procedure

In the event of a medical emergency, the PI and/or site investigator may require that the blind be broken for the participant experiencing the emergency when knowledge of the participant's treatment assignment may influence the participant's clinical care. Every effort will be made not to unblind the participant unless it is considered absolutely necessary for the welfare of the participant. Prior to unblinding, the investigator is encouraged (to the extent possible, without jeopardizing the participant's health) to contact the Sponsor (or designee) to discuss the decision to break the blind.

The PI and/or site investigator will be expected to provide a rationale for the necessity of unblinding, based on the expectation that knowledge of the participant's treatment assignment will have a meaningful impact on the participant's medical care in the short term. If a participant's treatment assignment is unblinded, the participant will remain in the study and continue with protocol-defined

study visits and procedures, unless there is another reason for participant discontinuation. The decision to unblind will be communicated to all regulatory bodies as required. At the end of the study, documentation of all unblinded participants (and the rationale for unblinding) will be incorporated into the trial master file.

### 6.6 Management of Pregnancy

All WOCBP will be monitored for the use of adequate contraception until completion of Visit 3. At Visit 3, WOCBP will have a pregnancy test and will be monitored for pregnancy until end of study Visit 4.

Any WOCPB who become pregnant during the study will be followed to term, and the following information will be gathered in regard to the pregnancy outcome: date of delivery and health status of the mother and child, including the child's gender, height, and weight. Complications and/or abnormalities must be reported, including any premature terminations. A pregnancy is reported as an AE or SAE only when there is suspicion that the investigational product may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy, including a spontaneous abortion or an elective termination for medical reasons. Pregnancies that occur up to Visit 3 (Day 29) will be included in the interim analysis (primary analysis) and the CSR, and any pregnancies that occur after Day 29 through Visit 4 and the outcome of pregnancies will be reported to the Sponsor as part of the safety management plan.

The PI is required to notify the Sponsor (or designee) within 24 hours of knowledge of a pregnancy.

### 6.7 Clinical Procedures

#### 6.7.1 Vital Signs

- Body temperature will be measured in degrees Celsius (recorded to the nearest 0.1 degree) by oral (sublingual) thermometer following at least 20 minutes of avoidance of food and drink.
- Respiratory rate will be measured in breaths per minute.
- Heart rate will be measured in beats per minute by automated device or manually, and not on the arm used for study vaccination in adults if an arm cuff is used.
- Blood pressure will be measured in millimeters (mm) of mercury by automated device or manually.
- Vital signs will be graded according to the toxicity grading scale in Appendix 3.

#### 6.7.2 Height and Weight

- Height will be measured in centimeters (cm) and recorded to the nearest 1 cm.
- Weight will be measured in kilograms (kg) and recorded to the nearest 0.1 kg.

#### 6.7.3 Complete Physical Examination

- A complete physical examination will include head, eyes, ears, nose, oropharynx, neck, chest

(auscultation), lymph nodes (neck, supraclavicular, axillary), back, abdomen (auscultation and palpation), musculoskeletal, skin (especially hands, arms, injection sites), and nervous system.

### 6.7.4 Injection Site Examination

- Redness will be examined under standard lighting conditions and measured based on the maximum diameter and recorded to the nearest 1 mm.
- Swelling will be examined by palpation and visual inspection under standard lighting conditions; the examiner may temporarily mark the skin at the margins of visible swelling, then measure at the maximum diameter and record the distance to the nearest 1 mm.
- Local reactions will be graded according to the toxicity grading scale in Appendix 2.

## 7. LABORATORY EVALUATIONS

Blood samples will be collected from all participants for immunogenicity testing and for safety testing.

### 7.1 Sample Collection, Distribution, and Storage

Samples to evaluate vaccine safety in adults will be obtained and processed at each trial site and transported to each site's clinical laboratory for testing. Research specimens collected for the immunogenicity endpoints will be separated into aliquots by each site's processing laboratory as per the Lab Manual and stored at <=-70°C in their storage facilities before being shipped to the central immunology laboratories (see Section 7.3). Continuous temperature monitoring and backup generators will be in place to ensure proper sample storage.

Volumes of blood required for adults are shown in Table 10. These volumes are for the expected standard laboratory testing; retesting may require additional blood draws. Provision for additional blood draws (for the purposes of safety assessments) will be included in the ICF.

**Table 10. Total Blood Volume Required (Adults)**

| **Category**<br>Tests | **Visit 0** | **Visit 1** | **Visit 2** | **Visit 3** | **Total** |
|---|---|---|---|---|---|
| **Hematology**<br>WBC, Hgb, Plts | 4 mL | - | 4 mL | - | **8 mL** |
| Chemistry<br>ALT, AST, creatinine | 3 mL | - | 3 mL | - | **6 mL** |
| **Pregnancy Test**[A]<br>hCG (serum or urine pregnancy test) | 5 mL | - | - | - | **5 mL**[C] |
| **Viral Serology**<br>HIV1/2 Ab, HBsAg, HCV Ab | 5 mL | - | - | - | **5 mL** |

| **Category**<br>Tests | **Visit 0** | **Visit 1** | **Visit 2** | **Visit 3** | **Total** |
|---|---|---|---|---|---|
| **Immunogenicity Assays**<br>Serotype-specific[B] IgG and OPA | - | 50 mL | - | 50 mL | **100 mL** |
| **Total Blood Volume** | **17 mL** | **50 mL** | **7 mL** | **50 mL** | **124 mL[C]** |

[A] In WOCBP only. Urine pregnancy test acceptable
[B] 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, 35B
[C] Maximum blood volume (assumes participant is a WOCBP)

Urine samples will be collected from WOCBP on Day 1 and Day 29 for pregnancy testing.

### 7.2 Clinical Laboratory Assays

Protocol-mandated screening and clinical safety laboratory tests in participants will be performed at site clinical labs, which provides Clinical Laboratory Improvement Amendments -certified comprehensive clinical laboratory services.

If clinically significant abnormalities are identified during screening, participants will be referred for further medical management. If identified during the study, participants may be asked to return to the study site for further evaluation, including clinical evaluation and repeat laboratory testing as warranted.

### 7.3 Immunological Assays

The following immunological assays are to be undertaken:

- IgG concentration: The serum IgG concentration to each of the 25 serotypes contained in IVT PCV-25- (1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, 35B) as well as serotype 6A, will be measured in a validated assay (E.g. ELISA, electrochemiluminescence immunoassay, meso scale discovery, etc.) in serum samples collected at Visits 1 and 3. [redacted]
- OPA: The functional activity of the serum antibody to each of the 25 serotypes contained in IVT PCV-25 (1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, 35B) as well as serotype 6A, will be determined in serum samples collected at Visits 1 and 3. This activity will be determined using the 4-fold multiplexed OPA (MOPA) developed at the [redacted] Alternative testing sites may be considered if the serotype-specific OPA assay has been validated.

### 7.4 Assay Qualification, Standardization, and Validation

Assays employed to evaluate the primary safety laboratory endpoint in adults have been properly validated and will be run with adequate controls. The IgG and MOPA that will be used to measure

the magnitude and the functional activity of the pneumococcal polysaccharide antibody responses constituting secondary endpoints of the trial are standardly used in the field to measure immunogenicity as a surrogate marker for efficacy of PCVs. The IgG has been [redacted] Both assays will be run with adequate controls.

### 7.5 Biohazard Containment

As transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and handling and shipping of all specimens for this study, as recommended by the US Centers for Disease Control and Prevention. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

## 8. SAFETY ASSESSMENT AND REPORTING

The PI is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol for the duration of the study.

### 8.1 Collection of Safety Events

AEs will be systematically collected at all study visits. Solicited AEs will be assessed in all participants immediately (30 minutes) after each vaccination. Subjects will record solicited AEs daily in the memory aid for the 7 days (Day 1 and the following 6 days) following vaccination, as well as record unsolicited AEs that occur prior to the 7- or 28-day follow-up visit (If a solicited AE is ongoing at 7 days post-vaccination, or occurs after 7 days post-vaccination, the event will be followed as per AE monitoring requirements. Clinically significant laboratory abnormalities in adult participants will also be recorded as an unsolicited AE.

SAEs will be recorded throughout the entire study period.

Medical events which occur between the time of enrollment (signed informed consent) and randomization for all participants regardless of screening outcome will be captured on the medical history form.

## 8.2 Definitions

### 8.2.1 Adverse Event

An AE, as defined in this protocol, is any untoward medical occurrence in a participant administered an investigational vaccine and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product. An AE will be documented as to whether or not it is considered to be related to study vaccine. An AE includes, but is not limited to, the following:

- An intercurrent illness or injury during the course of the study after receipt of an investigational product
- Any clinically significant worsening of a preexisting condition after receipt of an investigational product

A medical condition, in the form of signs, symptoms, disease, or laboratory or psychological/physiologic observations, occurring in a participant from whom consent has been obtained but prior to having received a study vaccine is not classified as an AE but will be captured and recorded on the medical history form.

### 8.2.2 Solicited AE

Solicited AEs are pre-specified local (injection-site specific) and systemic AEs that occur relatively more frequently, or are known to be associated with vaccination, and which are monitored actively as potential indicators of vaccine reactogenicity. Investigators will not be required to assess causality of solicited AEs if the onset is during the solicitation period.
The following specific solicited AEs will be monitored:

Local solicited AEs:

- Pain and/or tenderness
- Swelling
- Redness

Systemic solicited AEs:

- Fever (defined as body temperature ≥ 38°C)
- Headache
- Fatigue
- Myalgia
- Arthralgia
- Rash

### 8.2.3 Unsolicited AE

An unsolicited adverse event is any AE reported spontaneously by the participant, observed by the study staff during study visits, or those identified during review of medical records or source documents. Solicited AEs with an onset after the 7-day solicitation period will be considered unsolicited AEs. In the absence of a diagnosis, abnormal physical examination findings, or abnormal clinical safety laboratory test results that are assessed by the investigator to be clinically significant will be recorded as an AE.

### 8.2.4 Serious Adverse Event

An SAE is a specific AE that:

- Results in death.
- Is life-threatening.*
- Requires inpatient hospitalization or prolongation of an existing hospitalization.**
- Results in a persistent or significant disability or incapacity.***
- Results in a congenital anomaly or birth defect.

***Life-threatening** refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death but, as it actually occurred, did not create an immediate risk of death.

For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

****Hospitalization** is an admission to a health facility in the situation where there is an AE. A period of observation at a clinical trial site is not considered to represent hospitalization for the purposes of SAE reporting. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered a SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the PI on a SAE form. Such situations include, but are not limited to, the following:

- A hospitalization for a preexisting condition that has not worsened.
- Hospitalization for social reasons.

*****Disability** is defined as a substantial disruption in a person's ability to conduct normal life functions. If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-

threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias or convulsions that do not result in hospitalization.

### 8.2.5 Severity (Intensity) of an AE

The severity of all solicited AEs will be graded from Mild (Grade 1) to Potentially Life Threatening (Grade 4), based on the criteria given in Appendix 2. All AEs leading to death are Grade 5 events. AEs are graded based on the worst severity grade during the illness/symptoms. All other unsolicited AEs will be classified as an AE and graded based on the AE severity scale in Table 11 below. The grading scales for solicited and unsolicited AEs used in this study have been derived from the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events* (Version 2.1, July 2017), from the US National Institutes of Health, and from *Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*, U.S. Department of Health and Human Services, FDA, CBER, September 2007.

**Table 11. Severity Grading for Unsolicited AEs**

| Grade | Description |
|---|---|
| 1 | Causes no or minimal interference with normal daily activities; intervention not indicated |
| 2 | Interferes with but does not prevent normal daily activities; no or minimal medical intervention/therapy required |
| 3 | Prevents normal daily activities; intervention or hospitalization indicated |
| 4 | Causes inability to perform basic self-care activities (adults only); intervention indicated to prevent permanent impairment, persistent disability, or death |

### 8.2.6 Causal Relationship of an AE

A suspected adverse drug reaction (ADR) means any AE for which there is a reasonable possibility that the study vaccine caused the AE. A reasonable possibility means there is evidence to suggest a causal relationship between the vaccine and the AE. All cases judged by either the PI or the Sponsor (or designee) as having a reasonable suspected causal relationship to the study vaccine will qualify as ADRs. Medical judgment will be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, confounding factors such as concomitant medications, concomitant diseases, and relevant history.

The likelihood of the relationship of the AE to study vaccine is to be recorded as follows:

- Related: There is a reasonable causal relationship between the vaccine administered and the AE.
- Not Related: There is no reasonable causal relationship between the vaccine administered and the AE.

Note: solicited reactogenicity events will not be judged for relatedness.

### 8.2.7 Assessment of Outcome of AE

The outcome of the AE will be assessed and recorded as per the following categories:

- Ongoing.
- Recovered/resolved.
- Recovered/resolved with sequelae.
- Fatal.
- Unknown.

## 8.3 AE Recording and Reporting

All AEs will be recorded and reported after receipt of each study vaccine through 28 days post-vaccination (Visit 3). SAEs will be recorded throughout the entire study period.

The study staff must completely and promptly record each AE in the source documentation and on the relevant CRF, regardless of relationship to the vaccine administered or procedure as determined by the PI. The PI will attempt, if possible, to establish a diagnosis based on the signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the PI will report the diagnosis as the AE, not the signs and symptoms. AEs will be classified by the Medical Dictionary for Regulatory Activities (MedDRA) term and by severity, relatedness, and outcome.

Reporting of AEs will follow the regulatory guidelines of Health Canada, the local ethics committees (ECs), WCG IRB, and the PATH Office of Research Affairs (ORA) in regard to requirements, processes, and forms.

## 8.4 SAE Reporting

If an AE is classified as serious, an SAE form will be completed and submitted within 24 hours of the PI becoming aware of the SAE, including information on the location, severity, relatedness, and clinical summary of the event to the Sponsor (or designee) to initiate any DSMB evaluation, and any additional reporting requirements. The SAE submission will follow the regulatory guidelines of Health Canada, the local ECs, WCG IRB, and PATH ORA in regard to requirements, processes and forms. SAEs deemed related to study vaccine that are ongoing at the time of last participant last visit (LSLV) will continue to be followed until resolved, assessed to be resolved with sequelae, or assessed to be stable/chronic. SAEs deemed not related to study vaccine that are unresolved at the time of LSLV will be classified as ongoing.

### 8.4.1 Unanticipated Problems

Unanticipated problems will be submitted to Health Canada, the local ECs, WCG IRB, and PATH ORA per reporting requirements of each regulatory body. All serious unanticipated problems involving risk to participants or others will be promptly (within 48 hours) reported by telephone, by email, or by facsimile to the Sponsor (or designee). Follow-up reports will be submitted as soon as additional information becomes available.

## 9. SAFETY MONITORING

The PI will be responsible for continuous monitoring of all study participants' safety. In case of urgent need, participants will have the means to get in contact with study staff at any time (24 hours per day). The PI will also be available by cell phone 24-hours per day for medical emergencies. Weekly notifications of group-blinded Grade 3 or greater AEs will be sent to the PI, site investigators, CRO Medical Monitor, PATH Medical Officer (MO), and Inventprise's Chief Medical Officer (CMO) for situational awareness and ongoing safety assessment.

### 9.1 Data Safety Monitoring Board

A DSMB, composed of at least three independent members with expertise in vaccine clinical trials, will be convened to provide safety oversight. The DSMB will review unblinded safety and tolerability data after the last participant completes the 28-day follow-up visit (V3).

The DSMB will also meet on an ad hoc basis if a study pause rule is met (Section 9.2.) or upon the recommendation from the PI, PATH MO and Inventprise Inc.. In the event of a study pause, events will be unblinded, and no further enrollment will occur, and no study product will be administered until the DSMB approves lifting the pause.

DSMB reviews will indicate whether or not safety concerns were identified, and whether the trial should continue without change, be modified, or be terminated. The Sponsor will carefully consider the DSMB recommendations. If the Sponsor does not agree with these recommendations, a meeting will be held between the Sponsor CMO (or designee), PATH, PI, and DSMB to reach consensus on the appropriate action(s) to take in regard to the trial. However, if attempts to reach consensus fail, the Sponsor's opinion will prevail. In such situations, the Sponsor will inform Health Canada and local ECs of the Sponsor's perspective, and any changes to the trial.

The PI, PATH MO may also seek additional guidance from the DSMB as dictated by the occurrence of certain events that do not warrant a study pause.

The composition, responsibilities, and procedures of the DSMB will be detailed in the DSMB Charter.

### 9.2 Pause Rules

The DSMB will be convened if it is established that any of the following study pause rules has been met during the conduct of the trial:

- **Rule 1**: 1 or more participant experiences any vaccine-related Grade 4 AE or any vaccine-related SAE.
- **Rule 2**: 1 or more participant experiences Grade 3 or greater local reaction classified as related to vaccination by the PI: ulceration, necrosis, or sterile abscess at the injection site requiring drainage or surgical intervention.

  **Rule 3**: ≥ 5 participants in the same group inclusive of participants from Groups A, B, C, and D that experience the same Grade 3 (or greater) AE or laboratory abnormality attributed (related) to study vaccine. In the case of fever and pain at the injection site, the episode must last longer than 48 hours, and, in the case of fever, be confirmed by the PI without evidence of other medical causes.

### 9.3 Protocol Deviation

A protocol deviation is any nonconformity with the clinical trial protocol, GCP, SSP and site SOP requirements, or departure from planned study procedures or applicable regulatory requirements. Protocol deviations may be either on the part of the participant or the site staff/PI.

Protocol deviations are considered critical quality events if they significantly impact the completeness, accuracy, and/or reliability of the study data, or if they may significantly affect a participant's rights, safety, or well-being. Critical quality events must be reported to PATH within 24 hours of awareness. Examples of critical quality events may include failure to obtain informed consent, failure to report SAEs, enrolling participants in violation of key eligibility criteria designed to ensure a specific participant population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

When appropriate, corrective actions and preventive actions will be developed by the site to address critical quality events or deviations. These practices will be consistent with ICH E6 Guidelines.

## 10. DATA HANDLING AND RECORD KEEPING

The study monitors will visit the site at regular intervals, as per the Monitoring Plan, and perform pre-agreed source data verification of the data recorded in the 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system against the source documents available at the site. In addition, missing data forms and fields will be queried by electronic edit checks or through manual review of the data by the data management team. It is the PI's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the participant's EDC records and any supporting documentation. Study monitors will closely evaluate informed consents, inclusion/exclusion criteria, data entry timeliness, and visit dates and windows to ensure integrity of the study is maintained.

Any data discrepancies generated by the review will be flagged for the site staff to provide a satisfactory resolution. The data management team will review all the data discrepancy responses by the site to ensure the correctness of data. The medical history events and the AEs will be coded using MedDRA dictionary Version 24 or later and the concomitant medications will be coded using the WHO Drug Dictionary Version 2021 Sep 1 or later. After participants have completed all follow-up visits, and data coding and resolution of all the queries has been completed in the database, the database will be declared to be complete and accurate and will be locked for final statistical analysis of primary and secondary endpoints.

### 10.1 Case Report Form Development and Completion

Based on the final protocol of the study, a comprehensive set of CRFs will be prepared to capture all the relevant data required for analysis and reporting. This study will utilize a 21 CRF Part 11-compliant EDC system such that the entire study data can be maintained in a secure electronic system.

All study data will be collected by the clinical study staff using designated source documents and will be entered in the EDC system in an anonymized form. The study database will identify study participants by a unique study identification number(participant ID) and will not contain any identifying information such as name, address, or personal contact information, or any other regional/provincial/national identification number. CRFs will be reviewed by the clinical team who are responsible for ensuring that they are accurate and complete.

A thorough Data Management Plan (DMP) and corresponding database compliant with ICH requirements will be developed by the CRO. The appropriately trained site personnel will ensure that the study data recorded in the EDC system is verifiable with the source documents available at the site. To ensure that data are entered in a timely fashion so as to monitor safety of the study, it is expected that sites will maintain data entry within the timeframe specified in the study DMP.

The study sites will maintain the source documents for each study participant. The source documents and other supporting documents will be kept in a secure location. Source documentation will be available for review by the study monitor to ensure that the collected data are consistent with the CRFs.

### 10.2 Record Archival

#### 10.2.1 Archiving Data at Study Site

Study sites will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, sponsoring organization, and institutional requirements for the protection of confidentiality of participants. Sites will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. After completion of data coding and resolution of all the queries in the database, the database will

be declared to be complete and accurate and will be locked for final statistical analysis and made available to the Sponsor for long-term storage in a master file.

### 10.2.2 Data Storage and Archival

The sites will maintain an Investigator Site File, which will be used to file the IB, protocol, drug accountability records, correspondence with the EC, Sponsor (or designee), CRO, and other study-related documents. The PI will maintain, and store securely, complete, accurate, and current study records throughout the study.

As required by ICH GCP guidelines, the PI will keep essential documents until at least two years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the study product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The documents will be archived either at sites or at any other secure location as agreed upon with the Sponsor. It is the responsibility of the Sponsor to inform the PI/institution as to when these documents no longer need to be retained. Participants' medical records and other original data will be archived in accordance with the local regulations of the investigational sites.

## 10.3 Confidentiality

Documented evidence that the PI is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by the Sponsor and all data and information generated by the sites as part of the study (other than a participant's medical records) will be kept confidential by the PI and other study staff. This information and data will not be used by the PI or other study personnel for any purpose other than conducting the study.

# 11. STATISTICAL CONSIDERATIONS

## 11.1 Overview and General Considerations

This is a multicenter, randomized, active-controlled, observer-blind, Phase 2 trial in healthy pneumococcal vaccine-naïve male and non-pregnant female adult participants of age 18-49 years old.

No statistical hypothesis tests between treatment groups are planned in this study. All analyses for safety and immunogenicity data will be descriptive. All statistical analyses will be performed using SAS® software Version 9.2 or later.

Medical history and AEs will be coded using the current version of the MedDRA. Prior and concomitant medications will be coded using the current version of the WHO DD. Participant-wise data listing will be provided.

### 11.2 Randomization Procedures

The enrolled participants will be randomized in a ratio of 2:3:4:2 to receive IVT PCV-25 [redacted] IVT PCV-25 [redacted] IVT PCV-25 [redacted] or Prevnar 20™ , respectively with secure interactive response technology (IRT). An Interactive Web Response System (IWRS) will be the primary method of randomization, however a back-up randomization method will be available, if necessary. The study site(s) will be allocated blocks to maintain the randomization ratio(s) at each site. The randomization schedule will be prepared by the CRO statistician.

### 11.3 Sample Size and Power

220 eligible adult participants will be accrued. The sample size of this study is not based on any statistical hypothesis testing. The probabilities of observing at least one unsolicited AE, solicited local AE, or solicited systemic AE for various sample sizes in study groups when the true event rate is 0.5%, 1%, and 5%, respectively, are presented in Table 12 below.

**Table 12. Probability of Observing at Least One Unsolicited AE, Solicited Local AE, or Solicited Systemic AE by Assumed True Event Rates**

| Sample Size in Study Groups | Assumed True Event Rate | | |
|---|---|---|---|
| | 0.5% | 1.0% | 5% |
| N = 40 | 0.182 | 0.331 | 0.871 |
| N = 60 | 0.260 | 0.453 | 0.954 |
| N = 80 | 0.330 | 0.552 | 0.983 |

If the true AE rate is 5%, with 60 participants in a vaccine group, there is a 95% probability of observing at least one AE.

The expected precision of GMC ratio between the IVT PCV-25 and Prevnar 20 groups at the first (interim) analysis is presented in Table 13 below.

**Table 13. Expected Precision of GMC Ratio by Assumed Standard Deviation (SD) of $Log_{10}$ Antibody Concentration and GMC Ratio with Different Sample Sizes**

| Assumed SD of $log_{10}$ Antibody Concentration in IVT PCV-25 group | Assumed SD of $log_{10}$ Antibody Concentration in Prevnar 20 | Assumed GMC Ratio (IVT PCV-25 vs. Prevnar 20) | Expected 95% CI for GMC Ratio | | |
|---|---|---|---|---|---|
| | | | $N_1$:$N_2$ = 20:20 | $N_1$:$N_2$ = 30:20 | $N_1$:$N_2$ = 40:20 |

| | | | | | |
|---|---|---|---|---|---|
| 0.3 | 0.20 | 0.5 | 0.34-0.75 | 0.35-0.71 | 0.36-0.69 |
| | | 0.75 | 0.50-1.12 | 0.53-1.06 | 0.55-1.03 |
| | | 1.0 | 0.67-1.49 | 0.71-1.41 | 0.73-1.37 |
| | 0.25 | 0.5 | 0.32-0.77 | 0.34-0.73 | 0.35-0.72 |
| | | 0.75 | 0.49-1.15 | 0.51-1.10 | 0.52-1.07 |
| | | 1.0 | 0.65-1.54 | 0.68-1.47 | 0.70-1.43 |
| | 0.30 | 0.5 | 0.31-0.80 | 0.33-0.77 | 0.33-0.75 |
| | | 0.75 | 0.47-1.20 | 0.49-1.15 | 0.50-1.12 |
| | | 1.0 | 0.63-1.60 | 0.65-1.53 | 0.67-1.50 |
| 0.4 | 0.30 | 0.5 | 0.29-0.87 | 0.31-0.81 | 0.32-0.78 |
| | | 0.75 | 0.43-1.30 | 0.46-1.22 | 0.48-1.18 |
| | | 1.0 | 0.58-1.74 | 0.62-1.63 | 0.64-1.57 |
| | 0.35 | 0.5 | 0.28-0.90 | 0.30-0.85 | 0.31-0.82 |
| | | 0.75 | 0.42-1.35 | 0.44-1.27 | 0.46-1.23 |
| | | 1.0 | 0.56-1.80 | 0.59-1.69 | 0.61-1.64 |
| | 0.40 | 0.5 | 0.27-0.93 | 0.28-0.88 | 0.29-0.86 |
| | | 0.75 | 0.40-1.40 | 0.42-1.32 | 0.44-1.29 |
| | | 1.0 | 0.54-1.87 | 0.57-1.76 | 0.58-1.72 |
| 0.5 | 0.40 | 0.5 | 0.25-1.01 | 0.27-0.94 | 0.28-0.90 |
| | | 0.75 | 0.37-1.52 | 0.40-1.40 | 0.42-1.35 |
| | | 1.0 | 0.49-2.03 | 0.53-1.87 | 0.56-1.79 |
| | 0.45 | 0.5 | 0.24-1.05 | 0.26-0.97 | 0.27-0.94 |
| | | 0.75 | 0.36-1.58 | 0.38-1.46 | 0.40-1.41 |
| | | 1.0 | 0.48-2.10 | 0.51-1.95 | 0.53-1.88 |
| | 0.50 | 0.5 | 0.23-1.09 | 0.25-1.02 | 0.25-0.98 |
| | | 0.75 | 0.34-1.64 | 0.37-1.53 | 0.38-1.47 |
| | | 1.0 | 0.46-2.18 | 0.49-2.03 | 0.51-1.96 |
| 0.6 | 0.50 | 0.5 | 0.21-1.18 | 0.23-1.08 | 0.24-1.03 |
| | | 0.75 | 0.32-1.78 | 0.35-1.62 | 0.37-1.54 |
| | | 1.0 | 0.42-2.37 | 0.46-2.15 | 0.49-2.05 |
| | 0.55 | 0.5 | 0.20-1.23 | 0.22-1.12 | 0.23-1.07 |
| | | 0.75 | 0.31-1.84 | 0.33-1.68 | 0.35-1.61 |
| | | 1.0 | 0.41-2.45 | 0.45-2.25 | 0.47-2.15 |
| | 0.60 | 0.5 | 0.20-1.27 | 0.21-1.17 | 0.22-1.12 |
| | | 0.75 | 0.29-1.91 | 0.32-1.76 | 0.33-1.69 |
| | | 1.0 | 0.39-2.55 | 0.43-2.34 | 0.44-2.25 |

Note: CI = confidence interval; N1 is the sample size in the IVT PCV-25 group; N2 is the sample size in the Prevnar 20 group. An attrition rate of 10% was used in calculating the expected 95% CIs.

If the true SD of log10 antibody concentrations for a specific serotype is 0.5 in the IVT PCV-25 group and 0.45 in the Prevnar 20 group and the true GMC ratio between the two groups is 0.75, the expected two-sided 95% CI for the GMC ratio between the two groups is (0.45, 1.26) with 36 evaluable participants per group, (0.47, 1.19) with 54 evaluable participants in the IVT PCV-25 group and 36 evaluable participants in the Prevnar group, and (0.48, 1.16) with 72 evaluable participants in the IVT PCV-25 group and 36 evaluable participants in the Prevnar group.

## 11.4 Definitions of Populations to be Analyzed

### 11.4.1 Enrolled Population

All participants who provide written informed consent, regardless of the participant's screening, randomization, and treatment status in the study.

### 11.4.2 Exposed Population

All participants in the enrolled population who were randomized and received one vaccination dose (i.e., were accrued).

### 11.4.3 Safety Analysis Population

All participants in the exposed population for whom any safety data is available. All safety analyses will be performed using this population. The denominators for different safety endpoints may vary according to the number of participants with available data for the specific endpoint. For instance, the solicited local and systemic AE endpoint will be based only on those who have the corresponding CRF data regardless of other safety data. Treatment groups for safety analysis will be assigned according to the actual treatment received.

### 11.4.4 Full Analysis Population

All participants in the exposed population for whom any post-study vaccine administration immunogenicity results are available. An immunogenicity analysis will also be performed using this population. The analysis based on this population will serve as supportive results for all secondary immunogenicity objectives. Participants in the full analysis (FA) population will be analyzed as randomized, i.e., according to the treatment group to which participants were assigned.

### 11.4.5 Per Protocol Population

All participants in the FA population who were correctly vaccinated per randomization and have no protocol deviations that are determined to potentially interfere with the immunogenicity assessment of study vaccine.

The PP population will serve as the primary analysis population for the (secondary) immunogenicity analysis. The population will be adapted by assay; that is, a participant may be included in the PP population for IgG concentrations but not for OPA. The criteria (e.g., intake of prohibited medication expected to influence the immune response) for exclusion of participants from the PP population will be established before database lock for the final analysis and will be based on a blinded review of the data.

## 11.5 Estimands and Analytical Methodology

### 11.5.1 Estimands

The estimand corresponding to each primary and secondary objective is described in the table in Section 2.

For the primary safety estimand, receipt of concomitant medications will be handled with treatment policy strategy, which means that participants who take concomitant medications will be included in the safety analysis. The estimates will be calculated based on the safety analysis population.

For the estimand to evaluate the immunogenicity objective, receipt of immune-modifying medications/vaccines/treatments will be handled according to principal stratum strategy, which means participants who receive immune-modifying medications/vaccines/treatments will not be included in the primary immunogenicity analysis. The corresponding estimates will be computed based on both PP and Full Analysis populations, to examine robustness of the estimates. will be based on both PP and Full Analysis populations, to examine robustness of the estimates. Immunogenicity results that are below lower limit of quantification (LLOQ) will be set to half of LLOQ (LLOQ/2) in the analysis. Immunogenicity results above upper limit of quantification (ULOQ) will be set to ULOQ in the analysis.

### 11.5.2 Descriptive Methodology

When appropriate, continuous data will be summarized using descriptive statistics such as number of participants with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be presented using the percentage of participants in each category. A two-sided 95% CI will be provided for estimates, as appropriate. Individual participant data will be provided in listings.

### 11.5.3 Analysis Sequence

Upon completion of the Day 29 Visit 3 from all 220 participants, the CRO will prepare an unblinded safety report for review and approval by the DSMB to continue the study as planned.

The first analysis (interim) includes the dataset of the safety from all participants having completed the Day 29 visit, and the serotype-specific IgG responses from approximately 50% or more of the participants having completed the day 29 visit, in order to provide the Sponsor an initial indication of the comparative immunogenicity among the three different IVT PCV-25 formulations and to compare to the immune responses elicited in participants vaccinated with Prevnar 20$^{TM}$.

The second analysis includes the serotype-specific OPA results (individual participant ID-masked) and unblinded group-level results at baseline and Day 29 visit from all participants after OPA data become available.

For the first and second analyses, an independent CRO statistician and programmer team (whose responsibilities are otherwise limited to supporting the DSMB) will be unblinded to conduct the

analyses. Study unblinding will be conducted and documented in accordance with relevant CRO SOPs. The independent CRO statistician and programmer team will provide the unblinded group-level safety and immunogenicity report directly to the Sponsor, its consultants, PATH, the Bill & Melinda Gates Foundation, and the site investigators.

The independent CRO statistician and programmer team will provide the individual-level (participant ID masked) serotype-specific IgG and OPA responses to the Sponsor, its consultants, PATH, and the Bill & Melinda Gates Foundation. All other study personnel at the sites will remain blinded to individual treatment assignments until all participants complete Visit 4 and the database is locked.

When all safety data through Visit 4 from all 220 participants have been collected following the adult LSLV (Visit 4), the database will be cleaned and locked, and a final analysis including all late safety events and the complete IgG and OPA immunogenicity results from all participants will be performed. Detailed statistical analyses including tables, listings, and figures shells will be provided in a separate statistical analysis plan (SAP) which will be finalized prior to the interim analysis.

### 11.5.4 Analysis of Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, height, weight, sex, race, and ethnicity will be summarized for both the exposed and per protocol populations by treatment group.

For the exposed population, the number and percentage of participants with medical history will be tabulated by MedDRA System Organ Class (SOC), Preferred Term (PT) and treatment group. Using the WHO DD, the number and percentage of participants with concomitant medications will be tabulated by anatomical therapeutic chemical (ATC) classification, preferred drug name and treatment group.

Summaries of participant disposition will be prepared for all participants, including the number and percent enrolled, screened, randomized, and administered study vaccine, as well as a Consolidated Standards of Reporting Trials (CONSORT) diagram describing study participation and discontinuation. The reasons for screen failures and discontinuations will be summarized and listed.

A summary and listing of visit attendance will be prepared, in addition to a summary and listing of study vaccine administration and sample collection/availability for each sample.

### 11.5.5 Analysis of Primary Objective

All safety analyses will be conducted in the safety analysis population, according to the treatment received. Frequencies and percentages of participants with any solicited AE, solicited local AE, solicited systemic AE, unsolicited AE, clinical safety laboratory abnormality, SAE will be tabulated along with an exact two-sided 95% CI computed via the Clopper-Pearson method. The denominators for percentages will be the number of participants with the data available for analysis for the given endpoint. Participant-level data listing will be provided.

**Solicited local and systemic AEs**: All solicited AEs reported during 7 days post vaccination will be summarized according to defined severity grading scales. Frequencies and percentages of participants experiencing each solicited AE will be presented by treatment group and severity.

**Hematological and biochemical measurements**: For clinical safety laboratory data collected at screening and 7 days post-vaccination, individual Hgb, WBC count, Plts, AST, ALT, and creatinine values will be presented as number and percentage of participants out of range (above and below normal range as appropriate) and tabulated by toxicity grading and study group. In addition, summaries of changes from baseline will be presented. Clinically significant laboratory abnormalities will be considered an AE and relatedness will be reported.

**Unsolicited AEs**: All unsolicited AEs with onset occurring during the first 28 days post vaccination will be assessed for severity and relatedness to study product by the PI. Frequencies and percentages of participants with unsolicited AEs will be summarized by the SOC, PT, and treatment group. Similar summaries will be provided for severity and relatedness of the unsolicited AEs.

**SAEs**: All SAEs through Visit 4 (Day 169) will be recorded and summarized. Frequencies and percentages of participants with SAEs and relatedness to study vaccine of the events will be summarized by SOC, PT, and treatment group.

When an AE occurs more than once for a participant, the participant will be only counted once for the corresponding PT according to the maximum severity of the events. A summary table will be prepared for unsolicited AEs comprised of the following categories:

- Unsolicited AEs
- Related unsolicited AEs
- SAEs
- Related SAEs
- SAEs leading to death
- Unsolicited AEs leading to participant discontinuation

All reported AEs that start after vaccination will be tabulated. If a given disease/condition is already reported as ongoing at the first visit on the medical history form, it will be counted and tabulated as an AE only if it worsens after vaccination with the study vaccines.

Onset day, duration, and outcome of unsolicited AEs will be summarized by treatment group. For SAEs, seriousness criteria will be summarized as well.

### 11.5.6 Analysis of Secondary Objectives

The analysis of immunogenicity will be performed on the PP population as the primary analysis and the full analysis population as a secondary analysis.

Immunogenicity data will be descriptively analyzed. Serotype-specific IgG antibody responses will be measured at baseline (V1), and 28 days after study vaccination (V3).

- GMC with two-sided 95% CIs
- GMFR from baseline with two-sided 95% CI

Serotype-specific functional antibody responses will be measured by OPA and summarized at baseline (V1) and 28 days after study vaccination (V3),

- GMTs with two-sided 95% CIs,
- GMFR from baseline with 95% CI

GMCs and GMTs will be calculated for each treatment group along with their two-sided 95% CI, by exponentiating the corresponding log-transformed mean and their two-sided 95% confidence limits.

The ratio of the GMC/GMT between IVT PCV-25 formulations [redacted] to Prevnar 20™ and corresponding two-sided 95% CI will be provided. The log-transformed antibody responses will be used to construct a mean difference between the treatment groups and the comparator vaccine, Prevnar 20™ and its two-sided 95% CI using the two-sample t-test method. The mean difference and corresponding 95% CI will be back-transformed to obtain the GMC/GMT ratio between the two groups and corresponding 95% CI. An adjusted GMC/GMT ratio between the treatment groups will be also provided along with its two-sided 95% CI. The log-transformed antibody responses will be used to compute a mean difference between the two groups and corresponding two-sided 95% CI using analysis of covariance (ANCOVA) with log-transformed baseline antibody responses as a covariate. Other variables, such as age and sex, will be evaluated for inclusion in the ANCOVA model as well. The mean difference and its 95% CI will be exponentiated to obtain the adjusted GMC/GMT ratio between the two groups and corresponding 95% CI.

GMFRs and corresponding two-sided 95% CIs will be computed for each treatment group. The mean difference in the log-transformed antibody responses between 28 days post vaccination and baseline and corresponding two-sided 95% CI will be calculated using the paired t-test method and then back-transformed to obtain GMFR and its 95% CI. The two-sample t-test method will be used to obtain the two-sided 95% CI of the ratio of GMFRs between the study groups. Additionally, the distribution of the titers will be summarized using reverse cumulative distribution curves.

A secondary ad hoc analysis that combines the immunogenicity responses (IgG) from the Prevnar 20™ comparator vaccine participants in the Phase 1 (NCT05540028) trial ( n = 30 participants) will be added to the first 50% of participants (n = 20) in this trial and expressed as the ratio of the GMC

between of IVT PCV-25 formulations [redacted] and Prevnar 20$^{TM}$ in order to increase the precision in detecting relative serotype-specific differences between IVT PCV-25 and the comparator vaccine. The ad hoc analysis will occur at the time of the interim analysis.

### 11.6 Multiplicity

Due to the descriptive and exploratory nature of the analyses, no adjustment for multiplicity will be performed.

### 11.7 Handling of Participant Discontinuations and Missing Data

Missing immunogenicity data will not be imputed and will be analyzed as if they were missing randomly. Missing reactogenicity data will not be imputed. Missing AE dates will be imputed, and corresponding rules will be specified in the SAP. No other missing safety information will be imputed. Over the study period, the frequency and percentage of participants who discontinue from the study will be provided by treatment group. All participants who discontinue post-randomization will be further described regarding their time to and their reasons for discontinuation. For participants who discontinue from the study, their data collected before discontinuation will be analyzed under the analysis populations as applicable. If missing data rate for immunogenicity measures is higher than 20% or any patterns are spotted in the missing data, a sensitivity analysis will be outlined in the SAP to evaluate the robustness of the analysis results.

## 12. QUALITY ASSURANCE AND QUALITY CONTROL

### 12.1 General Considerations

The study will be conducted in full compliance with the protocol and ICH GCP to provide public assurance that the rights, safety, and well-being of study participants are protected, and that the clinical study data are credible. To ensure quality and standardization, SSPs will be developed for key protocol procedures .

All clinical testing sites in Canada will conduct the study guided by the protocol, SSPs, applicable site SOPs, and other written guidelines. Routine operational checks to verify that critical protocol requirements and procedures are executed correctly at the time the work is being performed will be conducted.

Prior to study initiation, the Sponsor and the designated CRO will conduct training on the protocol and applicable SOPs for the study staff.

The investigational sites will provide direct access to all study-related documents, source data/documents, and reports for monitoring and auditing by the Sponsor, and inspection by regulatory authorities.

## 12.2 External Monitoring

Sponsor monitoring responsibilities will be provided by the CRO. A site initiation visit will be conducted prior to beginning the study, and monitoring will be conducted at initiation, during, and at closeout of the study by the study monitor or designee. As appropriate and informed by risk assessment, remote monitoring activities may be considered in place of or to supplement onsite monitoring.

During the course of the study, the monitor will assess site activities at intervals to verify compliance to the protocol; completeness, accuracy, and consistency of the data and study product accountability; adherence to protocol and regulatory obligations; and to ensure that conduct of the research follows GCP. The monitor should have access to participant study records, study product accountability and other study-related records needed to verify the entries on the CRFs.

The PI and the monitor will cooperate to ensure that any problems detected in the course of these monitoring visits, including EDC completion and query resolution, are resolved in a predefined time frame described in the Clinical Monitoring Plan.

To ensure the quality of clinical data for all participants, a clinical data management review will be performed on participant data received by the CRO. During this review, participant data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. These reviews may include analysis of data quality (e.g., missing or inconsistent data, outlier data), identify data trend not easily detected by onsite monitoring, and performance metrics (e.g., screening or withdrawal rates, eligibility deviations, timeliness and accuracy of data submission). To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to sites for resolution as soon as possible and within the time frame described in the DMP; all queries must be resolved prior to database lock.

## 12.3 Independent Auditing

Sponsor representatives may audit the study to ensure that study procedures and data collected comply with the protocol and applicable SOPs of the site and the CRO, and that data are correct and complete. The PI will permit auditors to verify source data validation of the regularly monitored clinical study. The auditors will compare the entries in the CRFs with the source data and evaluate study sites for their adherence to the clinical study protocol and GCP guidelines and applicable regulatory requirements.

## 12.4 Regulatory Agency Auditing

The PI must be aware that representatives from regulatory authorities may wish to inspect the CRFs and associated study records. The PI will notify the Sponsor (or designee) within 24 hours following contact by a regulatory agency. The PI will make the relevant records available for inspection and will be available to respond to reasonable requests and audit queries made by authorized representatives of regulatory agencies. The PI will provide the Sponsor with copies of all

correspondence that may affect the review of the current study or their qualification as PI in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance in responding to regulatory audits or correspondence.

## 13. OBLIGATIONS AND ROLES OF THE SPONSOR, PI, AND STUDY PERSONNEL

This study will be conducted according to GCP as well as in accordance with Health Canada regulations. The Sponsor will ensure the trial is conducted in compliance with the protocol, GCP, and regulatory authority requirements. The Sponsor (or designee) will provide the PI with the funding and information needed to conduct the trial properly, ensuring proper monitoring of trial activities, and that the trial is conducted in accordance with the general investigational plan and protocol contained in the submissions to the regulatory authorities. The Sponsor will ensure that the PI and regulatory authorities are immediately informed (within 24 hours of the Sponsor becoming aware) of significant new adverse effects or risks with respect to the study vaccine. The Sponsor will ensure that they will be immediately informed (within 24 hours of awareness) of any other safety concerns which could influence decisions regarding informed consent, enrollment and vaccination in this trial.

In addition, the PI will follow local and institutional requirements including, but not limited to, investigational vaccines, clinical research, informed consent and ethics regulations. The Sponsor (or designee) will provide notification to the PI of protocol and amendment approvals by regulatory authorities when applicable. Any modifications to the research protocol, the ICF, and/or change in PI will be submitted for review and approval to regulatory authorities per their guidelines. The PI may deviate from the protocol without prior approval only when the deviation is necessary to eliminate an apparent immediate hazard to the study participant.

While the PI may delegate study duties to appropriate study personnel, the PI is ultimately responsible for the conduct of all aspects of the study.

## 14. ETHICAL CONSIDERATIONS AND INFORMED CONSENT

The study will be performed in accordance with ICH Guidelines for GCP E6 R2 (2018), Directive 2001/20/EC, which are consistent with the Ethical Guidelines outlined in the Declaration of Helsinki (2013), thus ensuring protection of the participants. The study will commence only after receipt of a favorable opinion from the ECs listed in this protocol and Health Canada.

### 14.1 Ethical Review

Ethical review of this study for the clinical site will be conducted by the local site ECs and WCG IRB. The PI is responsible for obtaining approval from the local site ECs, which will review and approve the protocol, the informed consent form, and any recruitment materials (advertising or informational material). PATH is responsible for obtaining approval from WCG IRB. This includes any modifications to these documents prior to, or during the study. Any change to the protocol or informed consent form must be reviewed and approved prior to implementation, except when

necessary to eliminate apparent immediate hazard to study participants. In such a case, the change must be later documented in an amendment and reported to the ECs as soon as possible. When a change involves only logistical or administrative aspects of the study, formal EC approval may not be required, but such amendments shall still be submitted to the ECs for information purposes, and the PI must provide the Sponsor with written confirmation that such logistical or administrative amendments have been submitted to the local ECs. The PI is also responsible for obtaining continuing review throughout the duration of the study in accordance with existing regulations.

### 14.2 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the participant's participation in the study. Before any study-related activities, the delegated study staff must ensure that the potential participant is fully informed about the objectives, procedures, potential risks, and potential benefits of study participation.

Potential subjects will be provided with the EC-approved ICF, allowed ample time to read the consent form, encouraged to ask questions about the study, have their questions answered and then be given time to decide about participation in the study. It will be emphasized that participation is voluntary and that they have the right to decline or discontinue at any time without giving any reason and without compromising rights in any way.

The delegated study staff must obtain the participant's voluntary, signed and dated ICF before any study-related procedures are performed. Study staff must document the informed consent process. The original, signed ICF must be kept in the site study file. A copy of the informed consent document will be given to the participant for their records.

### 14.3 Study-Related Injury

Participants will be informed that if they experience any severe illness, they should contact study staff as soon as possible, and they may be required to be evaluated at the study site depending on the AE. If participants seek medical care outside the study, they should inform the health care provider of their participation in this study. The Sponsor will cover all costs of care for study-related injury.

The Sponsor and implementing partner will both obtain and maintain appropriate and commercially reasonable amounts of insurance, including commercial general liability insurance, and product and completed operations liability insurance, including coverage for the clinical trial.

### 14.4 Risk/Benefit

It is expected that IVT PCV-25 will be well-tolerated based on the tolerability profile of the licensed PCVs and safety data from the Phase 1 CVIA 096 study. There are certain symptoms and signs, systemic or injection site, which have historically been associated with immunization generally, and if they do occur, usually are of mild or moderate intensity and transient in nature. Consequently, in early clinical trials of investigational vaccines, these symptoms and signs are typically considered

as risks and are solicited as potential AEs in the first week following immunization. In this trial, the solicited injection site AEs include pain (or tenderness), swelling, and erythema.

The solicited systemic AEs for the adult cohort are fever, headache, fatigue, myalgia, arthralgia, and rash.

It is expected that IVT PCV-25 will have an adequate safety profile based on the safety profile of the licensed PCVs. Since there may be unknown risks associated with the IVT PCV-25 vaccine, all participants will be monitored for any unsolicited AEs for 28 days following study vaccination and for any SAEs for the entire study period.

Hypersensitivity reactions may occur following the administration of any vaccine, including licensed vaccines, which in rare circumstances may be life-threatening. All participants will be informed in the ICF of this possibility following study vaccine administration and will be observed for a minimum of 30 minutes following study vaccine administration. Appropriate emergency medical treatment will be available in case of severe immediate reactions, such as anaphylaxis. Participants with a known hypersensitivity to any component of the study vaccine, or a history of hypersensitivity to any vaccine, will be excluded from the study.

Blood drawing- and venipuncture-associated risks may include minor bleeding or bruising at the venous access site, mild discomfort, upset stomach, dizziness, light-headedness, syncope, or very rarely infection. Blood samples will only be drawn by trained staff members, and medical assistance will be available in case of any complications. Subjects will be informed of these risks in the ICF, and participants will be in a seated or supine position during blood draws.

No benefits can be guaranteed to participants for their participation in this research study. Participants who participate in this study may benefit by being protected against pneumococcal disease caused by the additional serotypes contained in IVT PCV-25 that are not contained in Prevnar 20$^{TM}$.

Participants who participate in this study may benefit from the clinical assessments (e.g., medical history, physical examination, and routine clinical safety laboratory tests in adults) conducted at screening and during the study. If the participant is found to have any newly diagnosed medical condition or infection, the investigator will ensure that the participant is provided with appropriate and adequate referrals within the health care system. The information gained from this study may be useful in the development of a safe and effective 25-valent PCV. The known risks of participation in this study are believed to be outweighed by the potential benefits and value of the information to be gained.

### 14.5 Participant Confidentiality

Every effort will be made to protect participant privacy and confidentiality. Personal identifiers will not be included in any study reports. Medical records containing identifying information will be made available for review when the study is monitored by the Sponsor or an authorized regulatory

agency. Direct access may include examining, analyzing, verifying, and reproducing any records and reports that are important in the evaluation of the study.

All study-related information will be stored securely at the study sites. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process and administrative forms, and other reports will be identified only by a unique trial-related participant ID to maintain participant confidentiality. Laboratory reports may include the name and date of birth of the participant to minimize the risk of errors in the busy clinical laboratories. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for monitoring, or as required/permitted by law/regulatory authorities.

### 14.6 Reimbursement

Pending EC approval, participants will be compensated for their time and effort in this study. The study ICF will state the plan for reimbursement. Participants will not be charged for study vaccinations, research study visits, research-related examinations, or research-related laboratory tests.

### 14.7 Storage of Specimens

Stored study research samples will be labeled with a barcode that the study site can link to the study participant. All stored research samples will be recorded and any use documented. Samples may be stored at different repositories and laboratories to complete the analyses required to evaluate study primary and secondary objectives. As a part of the informed consent process, participants will be informed of and asked to agree to long-term storage of specimens for use in future, vaccine-related research.

When samples are no longer needed for the purposes of the study, they will be kept or destroyed, depending on whether participants consent to remaining samples being used in future vaccine-related research. Their use will be governed by a repository plan. No genetic testing will be done on the samples.

## 15. PUBLICATION POLICY

According to the policy of the International Committee of Medical Journal Editors (ICMJE) member journals, this clinical trial will be registered on clinicaltrials.gov.

The information generated in this study will be used by the Sponsor in connection with the development of the product and therefore may be disclosed to government regulatory agencies in various countries. The Sponsor (or designee) will prepare a clinical study report according to ICH-E3 guidelines. All partners recognize the importance of communicating study findings and therefore

will encourage their publication in reputable scientific journals and presentation at seminars or conferences, while protecting the integrity of the ongoing trial. Study results will be made publicly available in compliance with the WHO mandated timeframe for public disclosure of results from clinical trials. Any publication, lecture, manuscripts of the findings of this study by any individual involved with the study will be governed by the procedure outlined in the Clinical Trial Agreement. The ICMJE authorship criteria will be strictly followed for publication of any manuscripts arising from this trial. Within any presentation or publication, confidentiality of individual participants will be maintained.

# 16. APPENDICES

## 16.1 Appendix 1. Study Visits

| VISIT (study day) | V0 (D0) | V1 (D1) | V2 (D8) | V3 (D29) | V4 (D169)* |
|---|---|---|---|---|---|
| allowed window in days | -28 to 0 | 1 | V1+7 (+3) | V1+28 (+7) | V1+168 (+14) |
| Assign participant ID | ✓ | | | | |
| Demographics[A] | ✓ | | | | |
| Eligibility check | | ✓ | | | |
| Medical history[B] | ✓ | ✓ | ✓ | ✓ | ✓ |
| Concomitant medications | ✓[C] | ✓ | ✓ | ✓ | ✓ |
| Eligibility check | ✓ | | | | |
| Vital signs[D] | ✓ | ✓^✓ | ✓ | ✓ | |
| Complete physical exam[E] | ✓ | | | | |
| Targeted physical exam[F] | | ✓ | ✓ | ✓ | |
| Clinical chemistry[G] | ✓ | | ✓ | | |
| Hematology[H] | ✓ | | ✓ | | |
| Viral serology tests[I] | ✓ | | | | |
| Pregnancy test[J] (serum or urine) | ✓ | ✓ | | ✓ | |
| Randomization | | ✓ | | | |
| Administer study vaccine[K] | | ✓ | | | |
| Observation/solicited AEs | | ✓ | ✓ | | |
| Unsolicited AEs | | ✓ | ✓ | ✓ | |
| SAE | | ✓ | ✓ | ✓ | ✓ |
| Blood for immune testing | | ✓ | | ✓ | |
| Provide memory aid | | ✓ | | | |
| Review memory aid | | | ✓ | ✓ | |
| Exit study | | | | | ✓ |

* Telephone call "visit"

^ = Evaluations will be conducted twice – before and after vaccination

[A] Contact information, including home address, telephone number(s), and email address

[B] Complete medical history of relevance to study eligibility including vaccination history. V1-V4 to collect changes in medical condition during interval period between visits not captured on memory aid

[C] History of medication use in the past 28 days, and of medications taken that are of specific relevance to study eligibility (e.g., immunosuppressive medications)

[D] Temperature, pulse rate, respiratory rate, blood pressure

[E] Complete physical exam may be performed at either V0 or V1. Height and weight will be measured; a physical examination (PE) will be performed in all participants and include assessment of the major organ systems

[F] Targeted PE will be conducted only in the event of new symptom, sign or new AE; Injection site assessed at Visit 2

[G] Serum creatinine, ALT, AST

[H] WBC count, Hgb, Plts

[I] HIV 1/2 Ab, HBsAg, HCV Ab

[J] Women of childbearing potential (WOCBP) only. Serum pregnancy testing is preferred at V0 (D0) and urine pregnancy testing is acceptable. Urine will be collected at V1(D1) and V3 (D29) for pregnancy testing.

[K] Date and time documented

## 16.2 Appendix 2: Solicited Local and Systemic Reactions Toxicity Grading Tables: Adults

| Reaction | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| **Pain at injection site (tenderness)** | Does not interfere with activity / Mild discomfort to touch | Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity/Discomfort with movement | Any use of narcotic pain reliever or prevents daily activity / Significant discomfort at rest | Emergency room (ER) visit or hospitalization |
| **Redness at injection site**[a] | 2.5 – 5 cm | 5.1 – 10 cm | > 10 cm | N/A |
| **Swelling at injection site**[a] | 2.5 – 5 cm | 5.1 – 10 cm | > 10 cm | N/A |
| Ulceration, Secondary infection, Sterile abscess, Drainage and/or Necrosis | N/A | N/A | Presence of any reaction and confirmed by site investigator | N/A |
| **Fever (oral temp)** | 38.0 – 38.4°C | 38.5 – 38.9°C | 39.0 – 40°C | > 40°C |
| **Headache** | No interference with activity | Repeated use of non-narcotic pain reliever > 24 hours OR some interference with activity | Significant; any use Of narcotic pain reliever OR prevent daily activity | ER visit or hospitalization |
| **Fatigue** | No interference with activity | Some interference with activity | Significant; prevent daily activity | ER visit or hospitalization |
| **Myalgia** | No interference with activity | Some interference with activity | Significant; prevent daily activity | ER visit or hospitalization |
| **Arthralgia** | No interference with activity | Some interference with activity | Significant; prevent daily activity | ER visit or hospitalization |

| Reaction | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| **Rash** | Localized macular rash (not a local reaction at the site of injection) | Diffuse macular, maculopapular, or morbilliform rash OR target lesions | Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site | Extensive or generalized bulbous lesions OR Stevens-Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN) |

[a] Redness and swelling should be measured at greatest surface diameter in millimeters using a ruler.

## 16.3 Appendix 3: Vital Signs Toxicity Grading Table (Adults)

| Vital Signs[a] | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| **Fever – Temp (°C)** | 38.0 – 38.4°C | 38.5 – 38.9°C | 39.0 – 40°C | > 40°C |
| **Tachycardia – beats per minute** | 101 – 115 | 116 – 130 | > 130 | ER visit or hospitalization |
| **Bradycardia –beats per Minute** | 50 – 54 | 45 – 49 | < 45 | ER visit or hospitalization |
| **Hypertension (systolic) – mm Hg** | 141 – 150 | 150 – 165 | > 165 | ER visit or hospitalization |
| **Hypertension (diastolic) – mm Hg** | 91 – 99 | 100 – 105 | > 105 | ER visit or hospitalization |
| **Hypotension (systolic) – mm Hg** | 85 – 89 | 80 – 84 | < 80 | ER visit or hospitalization |
| **Respiratory Rate – breaths per minute** | 21 – 23 | 24 – 27 | > 27 | ER visit or hospitalization |

[a] Participant should be at rest for all vital sign measurements.

## 16.4 Appendix 4: Serum and Hematology Toxicity Grading Table

| **Serum** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
|---|---|---|---|---|
| Creatinine (mg/dL) | 1.1 – 1.3 x ULN | > 1.3 – 1.8 x ULN OR increase of > 0.3 above baseline | > 1.8 – < 3.5 x ULN OR increase of 1.5 – < 2.0 x above baseline | ≥ 3 .5 x ULN OR increase of > 2.0 x above baseline |
| Liver function tests – AST, ALT increased | 1.25 – < 2.5 x ULN | 2.5 – <5.0 x ULN | 5.0 – < 10.0 x ULN | ≥ 10.0 x ULN |
| **Hematology** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
| Hemoglobin [Female] (g/dL) | 11.0 – 12.0 | 9.5 – 10.9 | 8.0 – 9.4 | < 8.0 |
| Hemoglobin [Male] (g/dL) | 12.5 – 13.5 | 10.5 – 12.4 | 8.5 – 10.4 | < 8.5 |
| OR decrease Hemoglobin, change from baseline value (g/dL) | 1.0 – 1.5 | 1.6 – 2.0 | 2.1 – 5.0 | > 5.0 |
| WBC, increased (cell/$mm^3$) | 10,800 – 15,000 | 15,001 – 20,000 | 20,0001 – 25,000 | > 25,0000 |
| WBC, decreased (cell/$mm^3$) | 2,500 – 3,400 | 1,500 – 2,499 | 1,000 – 1,499 | < 1,000 |
| Platelets, decreased (cell/$mm^3$) | 100,000 – <125,000 | 50,000 – <100,000 | 25,000 – < 50,000 | < 25,000 |

Abbreviation: ULN = upper limit of normal range

Note: the laboratory values provided in this table serve as guidelines and are dependent upon institutional normal parameters.

Note: the severity grading scales used in this study are derived in part from *Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*, U.S. Department of Health and Human Services, FDA, CBER, September 2007, and the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events* (Version 2.1, July 2017), US National Institutes of Health.

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### 16.6 Appendix 6 Protocol Signature Page for Additional Investigators

## PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH-GCP guidelines as outlined in the 'Statement of Compliance.'

Signature of Site Principal Investigator Date

Name:

Title:

Organization: