

Report on the Deliberation Results

July 31, 2025

Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Capvaxive for Intramuscular Injection Syringes
Non-proprietary Name	Pneumococcal 21-valent Conjugate Vaccine (Conjugate with a Non Toxic Variant of Diphtheria Toxin)
Applicant	MSD K.K.
Date of Application	November 8, 2024

Results of Deliberation

In its meeting held on July 24, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is classified as a biological product. The re-examination period is 8 years. The vaccine product and its active substance are both classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

July 3, 2025

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Capvaxive for Intramuscular Injection Syringes
Non-proprietary Name	Pneumococcal 21-valent Conjugate Vaccine (Conjugate with a Non Toxic Variant of Diphtheria Toxin)
Applicant	MSD K.K.
Date of Application	November 8, 2024
Dosage Form/Strength	Injection: Each syringe (0.5 mL) contains 4 µg each of pneumococcal capsular polysaccharides of serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B (de- <i>O</i> -acetylated prior to conjugation), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B, individually conjugated to a nontoxic mutant of diphtheria toxin (CRM ₁₉₇).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Items Warranting Special Mention	None
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of disease caused by infection with *Streptococcus pneumoniae* in the elderly and in adults who are considered to be at increased risk for pneumococcal disease, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The product is classified as a biological product. The vaccine product and its active substance are both classified as powerful drugs.

Indication

Prevention of disease caused by infection with *Streptococcus pneumoniae* in the elderly and in adults who are considered to be at increased risk for pneumococcal disease.

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** The English translation has been corrected to reflect the corrections listed in the latest errata sheet (dated July 25, 2026) for the Japanese original.

Dosage and Administration

A single dose of 0.5 mL should be injected intramuscularly.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

May 23, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Capvaxive for Intramuscular Injection Syringes
Non-proprietary Name	Pneumococcal 21-valent Conjugate Vaccine (Conjugate with a Non Toxic Variant of Diphtheria Toxin)
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Date of Application	November 8, 2024
Dosage Form/Strength	Injection: Each syringe (0.5 mL) contains 4 µg each of pneumococcal capsular polysaccharides of serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B (de- <i>O</i> -acetylated prior to conjugation), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B, individually conjugated to a nontoxic mutant of diphtheria toxin (CRM ₁₉₇).

Proposed Indication

Prevention of disease caused by infection with *Streptococcus pneumoniae* (serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) in adults aged ≥50 years and in adults who are considered to be at increased risk for pneumococcal disease

Proposed Dosage and Administration

A single dose of 0.5 mL should be injected intramuscularly.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Streptococcus pneumoniae is a Gram-positive coccus classified into at least 100 serotypes based on the antigenicity of pneumococcal capsular polysaccharides (PnPs) and is a major respiratory pathogen (mBio. 2020;11:e00937-20). *Streptococcus pneumoniae* colonizes the nasopharyngeal mucosa. When progressing from the nasopharynx to the lower respiratory tract, it causes lower respiratory tract infections such as bronchitis and pneumonia. Pneumococcal disease is classified as either invasive pneumococcal disease (IPD), defined by detection of *Streptococcus pneumoniae* from normally sterile sites such as blood, cerebrospinal fluid, and synovial fluid, or non-invasive pneumococcal disease (non-IPD). According to the infectious disease trend surveillance in Japan, of the 1,398 patients with IPD reported in 2021 across all age groups, 279 patients (20.0%) were aged <5 years and 799 patients (57.2%) were aged ≥65 years, showing a bimodal age distribution (*Infectious Agents Surveillance Report* 2023;44:1-2). In addition to the infants and elderly, individuals with chronic heart, lung, liver, or kidney disease and those with autoimmune diseases are reported to be at increased risk of pneumococcal disease (*Vaccine*. 2016;34:4293-7, *Open Forum Infect Dis*. 2014;1:ofu024, etc.).

Pneumococcal vaccine products for the elderly and individuals who are considered to be at increased risk of disease caused by *Streptococcus pneumoniae* (high-risk individuals) approved for marketing to date in Japan are a 15-valent pneumococcal conjugate vaccine (PCV) (PCV15; brand name, Vaxneuvance Aqueous Suspension Syringes), 20-valent pneumococcal conjugate vaccine (PCV20; brand name, Prevenar 20 Suspension Liquid for Injection), and 23-valent pneumococcal polysaccharide vaccine (PPSV23; brand name, Pneumovax NP Syringes).

Capvaxive for Intramuscular Injection Syringes (hereinafter referred to as Capvaxive) is a pneumococcal 21-valent conjugate vaccine designed to address the major pathogenic serotypes, which were identified based on data on serotypes responsible for IPD in adults, and consisting of active substances of PnPs-diphtheria cross reactive material 197 (CRM₁₉₇) conjugates, which are from 6 serotypes (3, 6A, 7F, 19A, 22F, and 33F) shared with PCV15 and 15 serotypes unique to Capvaxive (8, 9N, 10A, 11A, 12F, 15A, de-*O*-acetylated polysaccharide from serotype 15B [deOAc15B], 16F, 17F, 20A, 23A, 23B, 24F, 31, and 35B). Based on results from clinical studies in healthy adults and high-risk adults conducted in and outside Japan, the applicant has submitted an application for marketing approval of Capvaxive for use in individuals aged ≥50 years and high-risk adults.

As of March 2025, Capvaxive has been approved for marketing for adults aged ≥18 years in 5 countries or regions including the US and Europe.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Active substances

CRM₁₉₇ used in the manufacture of the 21 serotype-specific monovalent bulk conjugate active substances is manufactured and controlled in the same manner as the CRM₁₉₇ used in the manufacture of PCV15. A description of CRM₁₉₇ is omitted because it has already been evaluated during the review of PCV15.

2.1.1 Generation and control of cell substrates

2.1.1.1 Generation and control of cell substrates of *Streptococcus pneumoniae*

Strains of *Streptococcus pneumoniae* serotypes 3, 6A, 8, 10A, 11A, 12F, 15B, 22F, and 33F were obtained from the University of Pennsylvania; serotype 7F from the State University of New York; serotypes 9N, 16F, 20A, and 23A from the American Type Culture Collection (ATCC); serotypes 15A, 17F, 19A, and 35B from the Food and Drug Administration (FDA) Bureau of Biologics; and serotypes 23B, 24F, and 31 from the University of Alabama at Birmingham. These strains were cultured in a biological material-free medium, from which master cell banks (MCBs) and working cell banks (WCBs) were established.

The MCBs and WCBs were subjected to release testing (culture purity, identification [colony morphology, Gram staining, optochin susceptibility, serological identification based on the quellung reaction¹⁾], and viable cell count). The results qualified these seed stocks. Of the 21 *Streptococcus pneumoniae* serotypes, 14 serotypes (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20A, 22F, and 33F) are also used in manufacture of active substances for PPSV23 or PCV15. Test results for these serotypes were submitted for approval review of PPSV23 or PCV15.

The MCBs are not planned to be regenerated, but new WCBs will be generated as needed.

2.1.2 Manufacturing process

The manufacturing process of the active substance (monovalent bulk conjugate) can be divided into manufacturing processes of CRM₁₉₇, PnPs, and the monovalent bulk conjugate.

- Manufacturing process of PnPs

The manufacturing process for PnPs of the 21 serotypes consists of seed culture, production culture, inactivation, clarification, ultrafiltration, polishing, recovery of the target substance, filling, and storage. The production culture, inactivation, ultrafiltration, polishing, and recovery of the target substance have been defined as critical steps.

The manufacturing process for PnPs of 14 serotypes (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20A, 22F, and 33F) is the same as that used for PPSV23 or PCV15, and process validation results obtained at a production scale had already been submitted during the review of applications for PPSV23 and PCV15. In addition, for manufacturing processes of PnPs for the remaining 7 serotypes (15A, 16F, 23A, 23B, 24F, 31, and 35B), process validations at a production scale have been conducted.

- Manufacturing process of monovalent bulk conjugate

Twenty-one serotype-specific monovalent bulk conjugate, active substances, are manufactured through a process consisting of dissolution of PnPs, PnPs degradation [REDACTED], ultrafiltration, PnPs activation, ultrafiltration, lyophilization, conjugation to CRM₁₉₇, [REDACTED], final ultrafiltration,

¹⁾ Of the 21 *Streptococcus pneumoniae* serotypes, 13 serotypes were included in this test using their MCBs and WCBs, whereas the remaining 8 serotypes (6A, 15A, 16F, 23A, 23B, 24F, 31, and 35B) were excluded. For the PnPs of each of the 21 serotypes, serotype identity is confirmed by nuclear magnetic resonance spectroscopy during the manufacturing process.

final filtration, final dilution, filling/storage, and testing. The PnPs activation, conjugation, [REDACTED], final ultrafiltration, final filtration, and final dilution have been defined as critical steps.

For manufacturing processes of the monovalent bulk conjugates, process validations at a production scale have been conducted.

2.1.3 Safety evaluation of adventitious agents

In the manufacturing process of PnPs for serotype [REDACTED], bovine-derived casamino acids (used in manufacture of endonuclease, which is added during the ultrafiltration step) are used as a biological raw material. Casamino acids are derived from milk obtained from healthy cows, manufactured through a process including inactivation and removal of potential pathogens, and confirmed to conform to the Standards for Biological Raw Materials.

2.1.4 Manufacturing process development

During development of active substances, changes were made to the manufacturing process. Major changes to the manufacturing process of the monovalent bulk conjugates involve manufacturing sites and scales as well as PnPs degradation for a part of the serotypes (processes before and after the changes are referred to as the pre-change process and proposed process). The vaccine product manufactured using active substance produced by the pre-change process was used in the phase I/II and phase I studies, whereas the vaccine product manufactured using active substance produced by the proposed process was used in the phase III studies.

In association with the process changes, comparability between the monovalent bulk conjugates before and after the changes was assessed in terms of quality attributes and thereby demonstrated.

2.1.5 Characterization

2.1.5.1 Structure and characterization

PnPs and the active substances (monovalent bulk conjugates) were subjected to characterizations presented in Table 1.

Table 1. Characterization items

PnPs	Structural analysis and physicochemical properties	Nuclear magnetic resonance spectroscopy, O-acetyl content (serotypes 7F, 11A, 15B, 16F, 17F, 20A, 22F, 31, 33F, and 35B), mean molecular weight, polysaccharide content, PnPs activation status (aldehyde content), and mean molecular weight of activated PnPs
Monovalent bulk conjugate	Structural analysis and physicochemical properties	Confirmation of covalent conjugation, mean molecular weight, polysaccharide/protein ratio, O-acetyl content (serotypes 7F, 11A, 16F, 17F, 20A, 22F, 31, 33F, and 35B), histidine content, polysorbate 20 concentration, and chloride concentration

2.1.5.2 Product-related substances/Product-related impurities

No product-related impurities of any PnPs have been identified. Product-related impurities identified in the monovalent bulk conjugates were free polysaccharides and free protein (derived from CRM₁₉₇). Free protein has been confirmed to be adequately removed during the manufacturing process. Free polysaccharides and free protein are controlled by the specifications for the active substances.

No product-related substances have been identified for either PnPs or the monovalent bulk conjugates.

2.1.5.3 Process-related impurities

Process-related impurities identified in PnPs were cell-derived C-polysaccharides, cell-derived proteins, cell-derived nucleic acids, organic solvents (ethanol, 2-propanol, and phenol), sodium acetate, polyethylenimine, tris(hydroxymethyl) aminomethane, and endonuclease (serotype **III**). Cell-derived proteins, cell-derived nucleic acids, polyethylenimine, tris(hydroxymethyl) aminomethane, and endonuclease (serotype **III**) have been confirmed to be adequately removed during the manufacturing process of PnPs, while cell-derived C-polysaccharides, organic solvents (ethanol, 2-propanol, and phenol), and sodium acetate have been confirmed to be adequately removed during the manufacturing processes of PnPs and the monovalent bulk conjugates. The levels of cell-derived proteins, cell-derived nucleic acids, and phenol are controlled by in-process control tests for PnPs.

Process-related impurities identified in the monovalent bulk conjugates were Impurity A, Impurity B, cyanide, Impurity C, Impurity D, and dimethyl sulfoxide (DMSO). Impurity A, Impurity B, Impurity C, Impurity D, and DMSO have been confirmed to be adequately removed during the manufacturing process. Cyanide (except for serotypes ■, ■, ■, and ■) is controlled by the specifications for the active substances.

2.1.6 Control of active substances

The active substances are controlled as serotype-specific monovalent bulk conjugates. The proposed specifications include description, identification (enzyme linked immunosorbent assay [ELISA]), pH, mean molecular weight measurement (high performance size exclusion chromatography [HPSEC]), polysaccharide/protein ratio (HPSEC), purity (free polysaccharides [HPSEC], free protein [micellar electrokinetic chromatography], residual cyanide [high performance liquid chromatography (HPLC)] [except for serotypes ■, ■, ■, and ■]), bioburden, bacterial endotoxins, and total polysaccharide content (HPSEC).

2.1.7 Stability of active substances

Table 2 shows main stability studies of active substances.

Table 2. Main stability studies of active substances

	Manufacturing process of active substances	No. of batches for each serotype	Storage condition	Study period	Storage form
Long-term	Proposed process	3	-80°C to -60°C	12, ^{a)} 18, ^{b)} or 24 months ^{c)}	
Photostability	Proposed process	1	Overall illumination of 1.2 million lx·hr or more, an integrated near ultraviolet energy of 200 W·h/m ² or more		██████████ bottle

[illegible]

b) Active substances for serotypes [REDACTED] and [REDACTED]. The stability study is ongoing for up to 120 months.

c) Active substances for serotypes [REDACTED] and [REDACTED]. The stability study is ongoing for up to 120 months.

Under the long-term storage condition, no clear changes were observed in quality attributes throughout the study period. The photostability testing showed that the active substances are photostable.

Based on the above, the following shelf lives have been proposed for active substances when stored in [REDACTED] bottles at -80°C to -60°C: 12 months for serotypes [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED] and [REDACTED], 18 months for serotypes [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED], and 24 months for serotypes [REDACTED] and [REDACTED].

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is an aqueous injection that contains PnPs-CRM₁₉₇ conjugate for each of the 21 serotypes at 4 µg as PnPs per syringe (0.5 mL). The excipients contained in the vaccine product are L-histidine, L-histidine hydrochloride hydrate, polysorbate 20, sodium chloride, hydrochloric acid, and water for injection. Capvaxive is presented in a pre-filled glass syringe and is thus a combination product classified as a drug.

2.2.2 Manufacturing process

The vaccine product is manufactured through a process consisting of formulation (preparation of [REDACTED] and [REDACTED], blending of active substances, bioburden-reduction filtration, and volume adjustment), filling (bioburden-reduction filtration, sterile filtration, and filling), testing, labeling, packaging, and storage.

The filling has been defined as a critical step.

For the manufacturing process of the vaccine product, a process validation at a production scale has been conducted.

2.2.3 Manufacturing process development

During development of the vaccine product, changes were made to the manufacturing process. Major changes involve vaccine formulation, filling container, manufacturing site, vaccine product scale, and manufacturing parameters (processes before and after the changes are referred to as the pre-change process and proposed process). The vaccine product manufactured through the pre-change process was used in phase I/II and phase I studies, and the vaccine product manufactured through the proposed process was used in phase III studies.

In association with the process changes, comparability between the vaccine products before and after the changes was assessed in terms of quality attributes and thereby demonstrated.

2.2.4 Control of vaccine product

The proposed specifications of the vaccine product include strength, description, identification (ELISA), pH, bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, polysorbate 20 content (HPLC), and assay (polysaccharide content [ELISA]).

2.2.5 Stability of vaccine product

Table 3 shows main stability studies of the vaccine product.

Table 3. Main stability studies of the vaccine product

	Manufacturing process of vaccine product ^{a)}	No. of batches ^{b)}	Storage condition	Study period	Storage form
Long-term	Proposed process	3	2°C-8°C	18 months ^{c)}	Glass syringe with a styrene butadiene or isoprene bromobutyl tip cap and bromobutyl plunger rubber stopper
Accelerated	Proposed process	3	25°C	14 weeks	
Photostability	Proposed process	1	Overall illumination of 1.2 million lx·hr or more, an integrated near ultraviolet energy of 200 W·h/m ² or more		

a) Active substances were manufactured through the proposed process.

b) Number of batches for each of [REDACTED] syringe and [REDACTED] syringe

c) The stability study is ongoing for up to 36 months.

Under the long-term storage condition, no clear changes were observed throughout the study period.

Under the accelerated condition, an increasing trend in insoluble particulate matter was observed, but in the other quality attributes, no clear changes were observed.

Photostability testing demonstrated that the vaccine product in the primary package alone was photolabile, whereas the vaccine product in the secondary package was photostable.

Based on the above, a shelf life of 18 months has been proposed for the vaccine product when filled in the primary package consisting of a glass syringe with a styrene butadiene or isoprene bromobutyl tip cap and bromobutyl plunger rubber stopper, protected from light, and stored at 2°C to 8°C.

2.3 Quality control strategy

Based on the following investigations, the quality control strategy was formulated. Because CRM₁₉₇ was previously evaluated during the review of PCV15, its description is omitted.

- Identification of critical quality attributes (CQAs)

The following quality attributes were identified as critical ones that may affect the efficacy and safety of Capvaxine:

- Active substance intermediates (PnPs)

[REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED]
[REDACTED], [REDACTED]
[REDACTED], [REDACTED]

- Active substances (the monovalent bulk conjugates)

[REDACTED], [REDACTED]
[REDACTED], [REDACTED], [REDACTED]
[REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED]
[REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED]
[REDACTED]

- Vaccine product

[REDACTED], polysorbate 20 content, polysaccharide content, [REDACTED], extractable volume, description, [REDACTED], [REDACTED], bacterial endotoxins, sterility, syringeability (delivery of fluid through a syringe injection needle), [REDACTED]

[REDACTED]

- Process characterization

During process characterization, each process parameter was assigned a risk level based on process knowledge, including manufacturing experience with PPSV23 and PCV15, which share manufacturing processes similar to those of Capvaxive for the PnPs/active substances and the vaccine product, together with risk assessments of quality attributes. Critical process parameters with a significant impact on CQAs were identified.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the active substances and vaccine product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Immunogenicity study in mice (CTD 4.2.1.1.1)

A vaccine containing PnPs-CRM₁₉₇ conjugates from 21 serotypes (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) (hereinafter referred to as V116) was administered intraperitoneally or intramuscularly to mice 3 times at intervals of 2 weeks to determine serotype-specific IgG antibody titers (electrochemiluminescent [ECL] method) and opsonophagocytic activity (OPA) antibody titers (multiplexed opsonophagocytic activity assay [MOPA]) in serum (Table 4).

Table 4. Immunogenicity study in mice

Study ID	Test system	Number of animals	Number of doses	Dosage regimen	Sampling points
MS-5B	Female mouse (Swiss Webster)	10/group	3	Intraperitoneal administration of 0.1 mL of V116 ^{a)b)} on Days 0, 14, and 28.	Day 0, 35
MS-10	Female mouse (CD-1)	10/group	3	Intramuscular administration of 0.1 mL of V116 ^{c)} on Days 0, 14, and 28.	Day 0, 35

a) Initial development batch. Vaccine containing antigens from the same 21 serotypes as Capvaxive, except that serotype 6A was replaced with serotype 6C

b) Vaccine containing 0.016, 0.08, 0.4, 2, or 4 µg of PnPs for each serotype per 0.1 mL

c) Vaccine containing 0.4 µg of PnPs for each serotype per 0.1 mL

In both studies, induction of serotype-specific IgG antibodies and OPA antibodies against all 21 serotypes contained in V116, as well as serotype 15B, was observed 1 week after the third dose of V116. V116 contains deOAc15B, which is structurally similar to serotype 15C. In both studies, cross-reactivity between serotype 15B and deOAc15B (15C) was observed. In Study MS-10, cross-reactivity between serotypes 6A and 6C was also observed. In Study MS-5B, antibody titers 1 week after the third dose of V116 were similar across serotypes in the high-dose groups (2 and 4 µg as PnPs for each serotype), whereas dose-dependent increases were observed for certain serotypes in the low-dose groups (0.016, 0.08, and 0.4 µg as PnPs for each serotype).

3.1.2 Immunogenicity studies in monkeys (CTD 4.2.1.1.2)

V116 was administered intramuscularly to rhesus monkeys, and serotype-specific IgG antibody titers (ECL method) and OPA antibody titers (MOPA) in serum were determined (Table 5).

Table 5. Immunogenicity studies in monkeys

Study ID	Test system	Number of animals	Number of doses	Dosage regimen	Sampling points
ARM-1	Male and female rhesus monkeys	8/group	3	Intramuscular administration of 0.25 mL of V116 ^{a,b)} on Days 0, 28, and 56.	Day 0, 14, 42, 70
ARM-3	Male and female rhesus monkeys	5/group	1	Intramuscular administration of 0.25 mL of V116 ^{b)} V116 ^{b)} + adjuvant, ^{c)} PCV13, PCV15, or PPSV23 on Day 0.	Day 0, 28

a) Initial development batch. Vaccine containing antigens from the same 21 serotypes as Capvaxive, except that serotype 6A was replaced with serotype 6C

b) Vaccine containing 1 µg of PnPs for each serotype per 0.25 mL

c) Adjuvant containing 62.5 µg of aluminum phosphate per 0.25 mL

In Study ARM-1, a single dose of V116 induced serotype-specific IgG antibody and OPA antibody against not only all 21 serotypes contained in V116, but also serotype 15B. Across most serotypes, serotype-specific IgG antibody titers and OPA antibody titers were similar 2 weeks after each of 3 doses of V116.

In Study ARM-3, serotype-specific IgG antibody titers and OPA antibody titers were generally comparable for serotypes shared by V116, PCV15, and 13-valent pneumococcal conjugate vaccine (PCV13). For serotypes shared by V116 and PPSV23, serotype-specific IgG antibody titers tended to be higher in the V116 group than in the PPSV23 group, whereas OPA antibody titers were generally comparable between the groups. Serotype-specific IgG antibody titers and OPA antibody titers were comparable between administration of V116 alone and administration of V116 with adjuvant.

3.1.3 Challenge study in mice (CTD 4.2.1.1.1)

In Study MS-5B (Table 4), 0.1 mL of V116³⁾ (containing 0.016, 0.08, 0.4, 2, or 4 µg as PnPs for each serotype) was administered intraperitoneally to Swiss Webster mice (10 females/group) 3 times at 2-week intervals. Three weeks after the third dose, animals in the V116 groups and a control group (not treated with V116; 10 females/group) were challenged intratracheally with a lethal dose (10^5 colony-forming unit [CFU]/animal) of *Streptococcus pneumoniae* (serotype 24F), and survival rates were evaluated. Although survival rates after exposure to *Streptococcus pneumoniae* were not dose-dependent, survival rates were higher in all V116 groups than in the control group.

In Study MS-10 (Table 4), 0.1 mL of V116 (containing 0.4 µg as PnPs for each serotype) was administered intramuscularly to CD-1 mice (10 females/group) 3 times at 2-week intervals. Three weeks after the third dose, animals in the V116 group and a control group (not treated with V116; 10 females/group) were challenged intratracheally with a lethal dose (10^5 CFU/animal) of *Streptococcus pneumoniae* (serotype 24F). As in Study MS-5B, survival rate was higher in the V116 group than in the control group.

3.1.4 T-cell response study in mice (CTD 4.2.1.1.4)

V116 (containing 0.8 µg of PnPs for each serotype per 0.1 mL) was administered intramuscularly to CD-1 mice 3 times at 4-week intervals. Two weeks after the third dose of V116, splenocytes were

³⁾ Initial development batch. Vaccine containing antigens from the same 21 serotypes as Capvaxive, except that serotype 6A was replaced with serotype 6C.

stimulated with CRM₁₉₇ peptides, and CRM₁₉₇-specific T-cell responses were evaluated using ELISpot and immunoassays.

Data obtained by the ELISpot assay showed increased numbers of T-cells producing IFN- γ , a T helper cell type 1 (Th1)-associated cytokine, and IL-4, a T helper cell type 2 (Th2)-associated cytokine, in the V116 group compared with the control group (untreated with V116). In addition, data obtained by immunoassay showed increased production of the Th1-associated cytokines IFN- γ and IL-2 and the Th2-associated cytokines IL-4, IL-5, IL-10, IL-1 β , and IL-12 p70 in the V116 group compared with the control group.

3.2 Safety pharmacology

No independent safety pharmacology studies of Capvaxive have been conducted. Safety pharmacology of Capvaxive was evaluated based on clinical observations and histopathological findings in a repeated intramuscular dose toxicity study in rats [see Section 5.2]. The applicant explained that there were no findings raising concerns about effects of V116 on physiological functions in the cardiovascular, respiratory, and central nervous systems.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that data on non-clinical pharmacology of Capvaxive have no particular problems.

3.R.1 Mechanism of action of Capvaxive

The applicant's explanation about the mechanism of action of Capvaxive:

Capvaxive is a pneumococcal conjugate vaccine consisting of PnPs from 21 serotypes conjugated to the CRM₁₉₇ carrier protein (PnPs-CRM₁₉₇ conjugates). The mechanism of action of pneumococcal conjugate vaccines involves T-cells specific to the carrier protein and B cells recognizing polysaccharides, ultimately inducing memory B cells via affinity maturation (*Nat Med.* 2011;17:1602-9, *Nat Rev Immunol.* 2009;9:213-20, etc.).

Administration of V116 in mice and rhesus monkeys induced serotype-specific IgG antibodies and serotype-specific OPA antibodies against not only all 21 serotypes included in Capvaxive, but also serotype 15B [see Section 3.1]. In mice, administration of V116 increased production of Th1- and Th2-associated cytokines, suggesting induction of carrier protein-specific T-cell responses. The observed expression of these cytokines was consistent with results obtained or reported with PCV15, indicating that Capvaxive can induce T-cell dependent memory B cells (*Vaccine.* 2017;35:865-72). Based on these non-clinical study results, Capvaxive is expected to prevent pneumococcal disease by inducing antibodies that enhance opsonization, phagocytosis, and killing of *Streptococcus pneumoniae*.

PMDA accepted the applicant's explanation about the mechanism of action of Capvaxive.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

For the present application, no non-clinical pharmacokinetic studies have been conducted.

The non-clinical study guidelines issued by the World Health Organization (WHO) (WHO Technical Report Series No. 927 Annex 1 Guidelines on Nonclinical Evaluation of Vaccines. WHO; 2005) and “Revision of the ‘Guidelines for Nonclinical Studies of Vaccines for Infectious Disease Prevention’” (PSB/PED Notification No. 0327-1, dated March 27, 2024) do not require the conduct of non-clinical pharmacokinetic studies for vaccines in general.

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted results from repeated-dose toxicity and reproductive and developmental toxicity studies of V116.

5.1 Single-dose toxicity

No single-dose toxicity studies of Capvaxive have been conducted. Toxicity of Capvaxive after a single-dose administration (acute toxicity) was evaluated based on results obtained after the first dose of V116 in a repeated-dose toxicity study in rats, and neither deaths nor changes in clinical signs were observed.

5.2 Repeated-dose toxicity

A repeated-dose toxicity study of V116 in rats was conducted (Table 6). Inflammation at the injection site was observed.

Table 6. Repeated-dose toxicity

Test system	Route of administration	Treatment period	Dose	Main findings ^{e)}	NOAEL	Attached document CTD
Male and female rats (Wistar)	Intramuscular ^{a)}	3 weeks (2 doses ^{b)}) + 4-week recovery	PBS or V116 ^{c)} 42 µg ^{d)}	Inflammation at the injection site ^{f)} Reversible	42 µg ^{d)}	4.2.3.2.1

a) A total of 0.5 mL was administered into quadriceps femoris muscles on both sides at 0.25 mL per site.

b) Administered on Days 1 and 22.

c) Vaccine product containing PnPs-CRM₁₉₇ conjugates at 84 µg /mL (as PnPs) in total and PnPs-CRM₁₉₇ conjugate of each serotype at 4 µg/mL (as PnPs), in a solution of 0.1% polysorbate 20, 150 mM sodium chloride, and 20 mM histidine (pH 5.8).

d) Indicated as a total dose of PnPs per body (µg/body)

e) On Day 15 or 36 in the V116 group, serotype-specific IgG antibody production was observed in 42% to 100% of animals for each of 19 serotypes of PnPs-CRM₁₉₇ conjugates (including the cross-reactive serotype 15B), excluding 3 serotypes (12F, 24F, and 23A).

f) The applicant explained that the finding in the V116 group was similar to that in the control group in terms of characteristics and severity and was not attributable to V116.

5.3 Genotoxicity

No genotoxicity studies of Capvaxive have been conducted.

5.4 Carcinogenicity

No carcinogenicity studies of Capvaxive have been conducted.

5.5 Reproductive and developmental toxicity

A fertility, embryofetal development, and postnatal development study of V116 in rats was conducted, and no effects of V116 on dams, embryos/fetuses, or offspring were observed (Table 7).

Table 7. Reproductive and developmental toxicity

Test system	Route of administration	Treatment period	Dose	Main findings	NOAEL	Attached document CTD
Female rat (Wistar)	Intramuscular	From 28 days before mating to Lactation Day 7 (4 doses in total ^{a)})	PBS or V116 ^{b)} 42 µg ^{c)}	Dams ^{d)} : None Embryos/fetuses ^{e)} : None F1 offspring ^{f)} : None	42 µg ^{c)}	4.2.3.5.2.1

- The vaccine product was administered at 1 site in either left or right quadriceps femoris muscle at 0.25 mL per site 28 and 7 days before mating, on Gestation Day 6, and on Lactation Day 7.
- Vaccine product containing PnPs-CRM₁₉₇ conjugates at 168 µg/mL (as PnPs) in total and PnPs-CRM₁₉₇ conjugate of each serotype at 8 µg/mL (as PnPs), in a solution containing 0.1% polysorbate 20, 150 mM sodium chloride, and 20 mM histidine (pH 5.8).
- Indicated as a total dose of PnPs per body (µg/body)
- On Gestation Day 21 or Lactation Day 21 in the V116 group, serotype-specific IgG antibody production was observed in 48% to 100% of dams for each of 19 serotypes of PnPs-CRM₁₉₇ conjugates, excluding 2 serotypes (12F and 24F).
- On Gestation Day 21 in the V116 group, serotype-specific IgG antibody production was observed in 40% to 100% of fetal serum pools for each of 10 serotypes of PnPs-CRM₁₉₇ conjugates, excluding 11 serotypes (6A, 10A, 12F, 15A, deOAc-15B, 20A, 23A, 23B, 24F, 33F, and 35B).
- On Lactation Day 21 in the V116 group, serotype-specific IgG antibody production was observed in 55% to 100% of F1 offspring for each of 16 serotypes of PnPs-CRM₁₉₇ conjugates, excluding 5 serotypes (10A, 12F, 23A, 24F, and 33F).

5.6 Local tolerance

Local tolerance of Capvaxive when administered intramuscularly was evaluated based on findings at the injection site in the repeated-dose toxicity study of V116 in rats [see Section 5.2]. The applicant explained that Capvaxive can be well tolerated locally for the following reasons: Although PnPs-CRM₁₉₇ conjugate concentration in the vaccine product used in the repeated-dose toxicity study was different from that in Capvaxive, both products have similar quality attributes (pH and osmolality) relevant to local irritation; and in the reproductive and developmental toxicity study using the test article with the same composition as Capvaxive [see Section 5.5], no findings related to the test article were observed at the injection site.

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about toxicity of Capvaxive is acceptable.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Biopharmaceutic studies and associated analytical methods

[illegible]

6.2 Clinical pharmacology

For the present application, the applicant did not submit data relating to clinical pharmacology.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from clinical studies listed in Table 8.

Table 8. List of main clinical studies for efficacy and safety

Region	Study	Phase	Population	Number of subjects vaccinated with the study drug	Outline of dosing regimen	Main endpoints
Japan	002	I	Pneumococcal vaccine-naïve healthy Japanese adults aged ≥ 20 years	Capvaxive group: 51 PPSV23 group: 51	Single intramuscular administration of Capvaxive 1.0 mL or PPSV23 0.5 mL	Safety
Foreign	001	I/II	Phase I part Pneumococcal vaccine-naïve healthy adults aged 18-49 years Phase II part Pneumococcal vaccine-naïve healthy adults aged ≥ 50 years	Phase I part Capvaxive 0.5 mL group: 30 Capvaxive 1.0 mL group: 30 PPSV23 group: 30 Phase II part Capvaxive group: 254 PPSV23 group: 254	Phase I part Single intramuscular administration of Capvaxive 0.5 or 1.0 mL or PPSV23 0.5 mL Phase II part Single intramuscular administration of Capvaxive 1.0 mL or PPSV23 0.5 mL	Safety Immunogenicity
Japan	009	III	Pneumococcal vaccine-naïve Japanese adults aged ≥ 65 years	Capvaxive group: 225 PPSV23 group: 225	Single intramuscular administration of Capvaxive or PPSV23 0.5 mL	Safety Immunogenicity
Foreign	003	III	Pneumococcal vaccine-naïve adults aged ≥ 18 years Cohort 1: ≥ 50 years Cohort 2: 18-49 years	Cohort 1 (≥ 50 years) Capvaxive group: 1,179 PCV20 group: 1,177 Cohort 2 (18-49 years) Capvaxive group: 200 PCV20 group: 100	Single intramuscular administration of Capvaxive or PCV20 0.5 mL	Safety Immunogenicity
Global	006	III	Adults aged ≥ 50 years with prior pneumococcal vaccination Cohort 1: With prior PPSV23 vaccination Cohort 2: With prior PCV13 vaccination Cohort 3: With prior PCV13 + PPSV23, PCV15 + PPSV23, PCV15, PCV20, or PPSV23 + PCV13 vaccination	Cohort 1 Capvaxive group: 229 (31 Japanese subjects) PCV15 group: 119 (19 Japanese subjects) Cohort 2 Capvaxive group: 174 (11 Japanese subjects) PPSV23 group: 85 (2 Japanese subjects) Cohort 3 Capvaxive group: 105	Single intramuscular administration of Capvaxive, PCV15, or PPSV23 0.5 mL	Safety Immunogenicity
Global	008	III	Pneumococcal vaccine-naïve high-risk adults aged 18-64 years	Capvaxive/saline group: 386 (31 Japanese subjects) PCV15/PPSV23 group: 130 (5 Japanese subjects)	Capvaxive/saline group: Intramuscular administration of Capvaxive 0.5 mL followed by saline 0.5 mL 8 weeks later PCV15/PPSV23 group: Intramuscular administration of PCV15 0.5 mL followed by PPSV23 0.5 mL 8 weeks later	Safety Immunogenicity
Foreign	007	III	Individuals with HIV infection aged ≥ 18 years regardless of prior pneumococcal vaccination history	Capvaxive/saline group: 156 PCV15/PPSV23 group: 157	Capvaxive/saline group: Intramuscular administration of Capvaxive 0.5 mL followed by placebo 0.5 mL 8 weeks later PCV15/PPSV23 group: Intramuscular administration of PCV15 0.5 mL followed by PPSV23 0.5 mL 8 weeks later	Safety Immunogenicity

7.1 Japanese phase I study (CTD 5.3.5.1.3, Study 002, study period, February to April 2021)

A randomized, double-blind,⁴⁾ parallel-group study was conducted at 2 study sites in Japan to investigate the safety, tolerability, and immunogenicity of Capvaxive in pneumococcal vaccine-naïve healthy Japanese adults aged ≥ 20 years (including those with stable chronic underlying diseases) (target sample size, 100 participants [50 per group]).

A single dose of Capvaxive⁵⁾ 1.0 mL or PPSV23 0.5 mL was intramuscularly administered.

All of randomized 102 participants (51 per group) received the study vaccine and were included in the safety analysis set.

Table 9 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events were assessed as adverse reactions.

Table 9. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 51)	PPSV23 (N = 51)
Local	54.9 (28)	66.7 (34)
Injection site pain	54.9 (28)	66.7 (34)
Injection site swelling	13.7 (7)	13.7 (7)
Injection site erythema	9.8 (5)	9.8 (5)
Systemic	23.5 (12)	27.5 (14)
Myalgia	17.6 (9)	19.6 (10)
Fatigue	13.7 (7)	9.8 (5)
Headache	9.8 (5)	9.8 (5)
Arthralgia	3.9 (2)	3.9 (2)
Pyrexia ^{a)}	0	5.9 (3)

Incidence % (n = number of participants with events), Medical dictionary for regulatory activities (MedDRA) version 24.0

a) Axillary temperature $\geq 37.5^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events and adverse reactions occurred in 66.7% (34 of 51) and 64.7% (33 of 51) of participants, respectively, in the Capvaxive group and in 68.6% (35 of 51) and 68.6% (35 of 51) of participants, respectively, in the PPSV23 group. Events reported by ≥ 4 participants in either group were injection site pain (30 participants in the Capvaxive group and 34 participants in the PPSV23 group), injection site swelling (9 and 7 participants, respectively), injection site erythema (9 and 5 participants, respectively), myalgia (9 and 10 participants, respectively), fatigue (7 and 5 participants, respectively), and headache (6 and 5 participants, respectively). A causal relationship to the study vaccine could not be ruled out for any of the above events.

There were no deaths, serious adverse events, or adverse events leading to study discontinuation.

7.2 Foreign phase I/II study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study 001, study period, December 2019 to July 2021)

A randomized, double-blind,⁴⁾ parallel-group study was conducted at 20 study sites (2 sites for the phase I part, 18 sites for the phase II part) in the US to investigate the safety, tolerability, and immunogenicity of Capvaxive in pneumococcal vaccine-naïve healthy adults (including those with stable chronic

⁴⁾ Study site staff engaged in control, preparation, and administration of study vaccines were unblinded.

⁵⁾ Polysaccharide content for each serotype: 4 $\mu\text{g}/1.0\text{ mL}$

underlying diseases) (target sample size, 90 participants [aged 18-49 years] for the phase I part [30 each in the Capvaxive 0.5 mL group, Capvaxive 1.0 mL group, and PPSV23 group] and 500 participants [aged ≥ 50 years] for the phase II part [250 each in the Capvaxive group and PPSV23 group]).

Phase I part

A single dose of Capvaxive⁵⁾ 0.5 mL or 1.0 mL or PPSV23 0.5 mL was intramuscularly administered.

All of randomized 90 participants (30 per group) received the study vaccine and were included in the safety analysis set.

Table 10 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events were assessed as adverse reactions.

Table 10. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive 0.5 mL (N = 30)	Capvaxive 1.0 mL (N = 30)	PPSV23 (N = 30)
Local	76.7 (23)	76.7 (23)	60.0 (18)
Injection site pain	73.3 (22)	76.7 (23)	56.7 (17)
Injection site swelling	20.0 (6)	16.7 (5)	13.3 (4)
Injection site erythema	10.0 (3)	23.3 (7)	20.0 (6)
Systemic	43.3 (13)	46.7 (14)	36.7 (11)
Headache	30.0 (9)	20.0 (6)	16.7 (5)
Myalgia	26.7 (8)	30.0 (9)	13.3 (4)
Fatigue	26.7 (8)	26.7 (8)	16.7 (5)
Arthralgia	16.7 (5)	10.0 (3)	6.7 (2)
Pyrexia ^{a)}	0	0	0

Incidence % (n), MedDRA version 23.0

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events and adverse reactions occurred in 76.7% (23 of 30) of participants and 76.7% (23 of 30) of participants in the Capvaxive 0.5 mL group, 80.0% (24 of 30) of participants and 80.0% (24 of 30) of participants in the Capvaxive 1.0 mL group, and 73.3% (22 of 30) of participants and 66.7% (20 of 30) of participants in the PPSV23 group. Events reported by ≥ 4 participants in any group were all solicited adverse events and included injection site pain (22 participants in the Capvaxive 0.5 mL group, 23 participants in the Capvaxive 1.0 mL group, and 17 participants in the PPSV23 group), headache (10, 6, and 5 participants, respectively), myalgia (8, 9, and 4 participants, respectively), fatigue (8, 8, and 5 participants, respectively), injection site swelling (6, 5, and 4 participants, respectively), arthralgia (5, 3, and 2 participants, respectively), and injection site erythema (3, 7, and 6 participants, respectively). Of these events, a causal relationship to the study vaccine could not be ruled out for all local adverse events, as well as for myalgia (8 participants in the Capvaxive 0.5 mL group, 9 participants in the Capvaxive 1.0 mL group, and 4 participants in the PPSV23 group), fatigue (7, 8, and 4 participants, respectively), headache (7, 6, and 2 participants, respectively), and arthralgia (5, 3, and 2 participants, respectively).

There were no deaths, serious adverse events, or adverse events leading to study discontinuation.

Phase II part

A single dose of Capvaxive⁵⁾ 1.0 mL or PPSV23 0.5 mL was intramuscularly administered.

Of the 510 randomized participants⁶⁾ (254 in the Capvaxive group, 256 in the PPSV23 group), 508 participants (254 in the Capvaxive group, 254 in the PPSV23 group) received the study vaccine and were included in the safety analysis set, excluding 2 participants in the PPSV23 group. Among all randomized participants, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the per-protocol (PP) population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoint was “serotype-specific OPA geometric mean titer (GMT) at Day 30 after the study vaccination,” and the results are as shown in Table 11.

Table 11. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (N = 254)		PPSV23 (N = 254)		GMR [two-sided 95% CI] ^{a)}
	No. of participants	OPA GMT [two-sided 95% CI] ^{a)}	No. of participants	OPA GMT [two-sided 95% CI] ^{a)}	
12 shared serotypes					
3	252	226.3 [196.3, 260.8]	254	226.2 [196.0, 261.0]	1.00 [0.82, 1.22]
7F	252	3535.4 [2953.1, 4232.5]	254	2906.8 [2425.3, 3483.8]	1.22 [0.95, 1.56]
8	252	1504.7 [1303.3, 1737.2]	254	1526.8 [1320.7, 1764.9]	0.99 [0.80, 1.21]
9N	252	10327.1 [8588.5, 12417.8]	254	9106.3 [7561.2, 10967.2]	1.13 [0.87, 1.47]
10A	252	6062.2 [5092.8, 7216.2]	254	5092.1 [4255.6, 6092.9]	1.19 [0.93, 1.52]
11A	252	2840.4 [2385.9, 3381.4]	254	1252.3 [1049.5, 1494.2]	2.27 [1.78, 2.90]
12F	252	2549.4 [2028.4, 3204.3]	254	991.1 [787.0, 1248.2]	2.57 [1.86, 3.55]
17F	252	18394.1 [15076.4, 22442.0]	254	11249.9 [9205.1, 13749.0]	1.64 [1.24, 2.16]
19A	252	2388.1 [2028.1, 2812.0]	254	2116.1 [1794.3, 2495.8]	1.13 [0.90, 1.41]
20A	252	9305.3 [7751.7, 11170.3]	254	5068.0 [4215.6, 6092.8]	1.84 [1.43, 2.36]
22F	252	8213.6 [6553.8, 10293.7]	254	5192.2 [4135.1, 6519.5]	1.58 [1.16, 2.16]
33F	252	28129.2 [22954.0, 34471.2]	254	29974.6 [24388.0, 36840.8]	0.94 [0.71, 1.24]
9 non-shared serotypes					
6A	252	2757.5 [2129.4, 3571.0]	254	457.0 [351.9, 593.4]	6.03 [4.23, 8.62]
15A	252	11640.0 [9787.7, 13842.8]	254	1711.4 [1434.0, 2042.5]	6.80 [5.37, 8.62]
15C	252	12611.8 [10473.3, 15186.8]	254	4200.7 [3476.1, 5076.5]	3.00 [2.31, 3.90]
16F	252	9820.7 [7641.8, 12620.9]	254	539.2 [417.2, 696.8]	18.21 [12.98, 25.57]
23A	252	11554.5 [8567.7, 15582.4]	254	593.9 [435.9, 809.2]	19.45 [12.87, 29.40]
23B	252	3137.2 [2392.1, 4114.3]	254	105.0 [79.8, 138.2]	29.88 [20.72, 43.09]
24F	252	7640.8 [5917.0, 9866.8]	254	238.7 [182.7, 311.7]	32.02 [22.83, 44.89]
31	252	4462.0 [3422.6, 5817.0]	254	127.8 [97.3, 167.9]	34.90 [24.25, 50.23]
35B	252	15704.6 [13151.1, 18754.0]	254	1745.2 [1459.0, 2087.4]	9.00 [7.19, 11.26]

a) GMT, GMT ratio, and two-sided 95% CI were calculated using a constrained longitudinal data analysis (cLDA) model. This model used natural log-transformed antibody titers at baseline and at Day 30 postvaccination as response variables and included timepoint, vaccine group, the interaction between timepoint and vaccine group, age category (50-64 years, 65-74 years, ≥75 years), and the interaction between timepoint and age category. An unstructured covariance matrix was used to model correlations among repeated measurements.

Table 12 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events were assessed as adverse reactions.

⁶⁾ Randomization was performed using age at randomization (50-64 years, 65-74 years, ≥75 years) as a stratification factor.

Table 12. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 254)	PPSV23 (N = 254)
Local	51.2 (130)	40.9 (104)
Injection site pain	46.5 (118)	37.8 (96)
Injection site swelling	11.0 (28)	7.9 (20)
Injection site erythema	8.7 (22)	6.7 (17)
Systemic	34.6 (88)	29.5 (75)
Fatigue	19.3 (49)	12.2 (31)
Headache	16.9 (43)	13.4 (34)
Myalgia	11.0 (28)	9.4 (24)
Arthralgia	4.3 (11)	4.3 (11)
Pyrexia ^{a)}	0.4 (1)	0.4 (1)

Incidence % (n), MedDRA version 24.0

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events occurred in 66.5% (169 of 254) of participants in the Capvaxive group and 59.4% (151 of 254) of participants in the PPSV23 group. Events reported by ≥ 4 participants in either group were injection site pain (118 participants in the Capvaxive group and 96 participants in the PPSV23 group), headache (51 and 48 participants, respectively), fatigue (50 and 34 participants, respectively), myalgia (34 and 28 participants, respectively), injection site swelling (30 and 20 participants, respectively), injection site erythema (26 and 17 participants, respectively), arthralgia (15 and 14 participants, respectively), back pain (5 and 5 participants, respectively), diarrhoea (5 and 5 participants, respectively), COVID-19 (4 and 2 participants, respectively), nausea (3 and 6 participants, respectively), oropharyngeal pain (3 and 7 participants, respectively), cough (1 and 5 participants, respectively), and nasal congestion (0 and 4 participants, respectively).

Within 30 days after the study vaccination, adverse reactions occurred in 34.3% (87 of 254) of participants in the Capvaxive group and 26.8% (68 of 254) of participants in the PPSV23 group. All of the local adverse events were assessed as adverse reactions, and systemic adverse reactions reported by $\geq 5\%$ of participants in either group were fatigue (45 participants in the Capvaxive group and 28 participants in the PPSV23 group), headache (44 and 32 participants, respectively), and myalgia (25 and 18 participants, respectively).

An adverse event leading to death occurred in 1 participant in the Capvaxive group (COVID-19⁷⁾), but a causal relationship to Capvaxive was ruled out for the event.

During the study period, serious adverse events occurred in 1.6% (4 of 254) of participants in the Capvaxive group (atrial fibrillation, COVID-19, cervical radiculopathy, gastrointestinal haemorrhage, and rotator cuff syndrome in 1 participant each; some participants had multiple events) and 1.2% (3 of 254) of participants in the PPSV23 group (acute coronary syndrome, acute kidney injury, Staphylococcal bacteraemia, and urinary tract infection in 1 participant each; some participants had multiple events), but their causal relationship to the study vaccine was ruled out.

No adverse events leading to study discontinuation occurred.

⁷⁾ 71-year-old female. Medical history of gastroesophageal reflux disease, hypercholesterolaemia, insomnia, etc. On Day 24 after vaccination of Capvaxive, she presented to hospital with pyrexia, nausea, dizziness, weakness, and shortness of breath lasting 3 days and was hospitalized with a diagnosis of severe COVID-19. On the following day, artificial respiration was indicated for respiratory failure, and she died on Day 28 after the study vaccination. No autopsy was performed. A causal relationship to the study vaccine was ruled out.

7.3 Phase III studies

7.3.1 Japanese phase III study (CTD 5.3.5.1.8, Study 009, study period, January to May 2023)

A randomized, double-blind,⁴⁾ parallel-group study was conducted at 8 study sites in Japan to investigate the safety, tolerability, and immunogenicity of Capvaxive in pneumococcal vaccine-naïve Japanese adults aged ≥ 65 years (including those with stable chronic underlying diseases) (target sample size, 440 participants [220 each in the Capvaxive group and PPSV23 group]⁸⁾).

A single dose of Capvaxive⁹⁾ or PPSV23 0.5 mL was intramuscularly administered.

All of randomized¹⁰⁾ 450 participants (225 each in the Capvaxive group and PPSV23 group) received the study vaccine and were included in the safety analysis set. Among all randomized participants, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the PP population. All participants who received the study vaccine were included in the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoints were “serotype-specific OPA GMTs at Day 30 after the study vaccination” and “serotype-specific OPA responder rate at Day 30 after the study vaccination (the proportion of participants with a ≥ 4 -fold rise in OPA titer from baseline to Day 30 after study vaccination). The following criteria (i), (ii), and (iii) were specified for demonstration of non-inferiority ([i]) and superiority ([ii] and [iii]) of Capvaxive to PPSV23:

- (i) For 12 shared serotypes and cross-reactive serotype 15B, the lower bound of the 95% confidence interval (CI) of the ratio of serotype-specific OPA GMT at Day 30 after the study vaccination in the Capvaxive group to that in the PPSV23 group (GMR) exceeds 0.5.
- (ii) For non-shared serotype 15C, the lower bound of the 95% CI of the serotype-specific OPA GMR at Day 30 after the study vaccination exceeds 1.0.
- (iii) For 8 non-shared serotypes excluding the serotype 15C, the lower bound of the 95% CI of difference in serotype-specific OPA responder rate (%) at Day 30 after the study vaccination between the Capvaxive group and PPSV23 group exceeds 0%.

For immunogenicity, Table 13 shows serotype-specific OPA GMTs at Day 30 after the study vaccination in the Capvaxive group and PPSV23 group. For all of the 12 shared serotypes and cross-reactive serotype 15B, the (i) non-inferiority criterion was met, and for non-shared serotype 15C, the (ii)

⁸⁾ In view of results from a subgroup aged ≥ 65 years in the Japanese phase I study (Study 002), the sample size of 200 participants per group was calculated to simultaneously demonstrate all the following (i) to (iii) in terms of OPA GMT and OPA responder rate, the primary endpoints, by tests at a one-sided significance level of 0.025 with a power of approximately 95% on hypotheses listed below: (i) Non-inferiority of Capvaxive to PPSV23 for 12 shared serotypes and cross-reactive serotype 15B (non-inferiority margin of 0.5 for OPA GMR); (ii) superiority of Capvaxive to PPSV23 for non-shared serotype 15C (superiority margin of 1.0 for OPA GMR); and (iii) superiority of Capvaxive to PPSV23 for 8 non-shared serotypes excluding serotype 15C (superiority margin of 0% for the difference in OPA responder rate between Capvaxive and PPSV23). On the assumption that 10% of participants would be excluded from the evaluable population, the target sample size of 220 participants per group was specified.

- For (i), GMR (Capvaxive/PPSV23) ranges from 1.11 to 3.02, and the standard deviation of natural log-transformed antibody titers ranges from 1.00 to 1.88.
- For (ii), GMR (Capvaxive/PPSV23) is 2.88, and the standard deviation of natural log-transformed antibody titers is 1.67.
- For (iii), the OPA responder rate in the Capvaxive group ranges from 58.8% to 87.9%, which exceeds that in the PPSV23 group by 17.6% to 67.7%.

⁹⁾ Polysaccharide content for each serotype: 4 μ g/0.5 mL

¹⁰⁾ Randomization was performed using the age category (65-74 years, 75-84 years, or ≥ 85 years) as a stratification factor.

superiority criterion was met. Table 14 shows serotype-specific OPA responder rates at Day 30 after the study vaccination in the Capvaxive group and PPSV23 group. For all of the 8 non-shared serotypes, the (iii) superiority criterion was met. All of the (i) to (iii) criteria were met, and the primary immunogenicity objective was achieved.

Table 13. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (N = 225)		PPSV23 (N = 225)		GMR [two-sided 95% CI] ^{a)}
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	
12 shared serotypes					
3	224	157.3 [134.3, 184.3]	224	167.9 [143.3, 196.7]	0.94 [0.75, 1.17]
7F	225	2648.7 [2284.5,3070.9]	225	2442.6 [2106.1,2832.9]	1.08 [0.88, 1.33]
8	225	1289.9 [1126.8,1476.6]	225	1148.6 [1002.2,1316.4]	1.12 [0.93, 1.36]
9N	222	2853.5 [2461.2,3308.4]	222	2709.5 [2343.7,3132.3]	1.05 [0.86, 1.29]
10A	224	1493.8 [1232.9,1809.9]	224	904.9 [746.3, 1097.3]	1.65 [1.28, 2.14]
11A	224	1288.8 [1086.6,1528.6]	224	849.9 [715.5, 1009.6]	1.52 [1.20, 1.92]
12F	225	984.9 [781.8, 1240.7]	224	500.2 [395.9, 632.1]	1.97 [1.43, 2.72]
17F	224	3056.4 [2596.3,3597.9]	224	1911.1 [1623.5,2249.8]	1.60 [1.28, 2.00]
19A	225	1328.9 [1120.4,1576.2]	225	1148.3 [967.5,1362.9]	1.16 [0.93, 1.45]
20A	222	2576.1 [2212.4,2999.5]	224	1784.0 [1526.1,2085.4]	1.44 [1.18, 1.77]
22F	225	1810.4 [1527.2,2146.1]	224	1301.8 [1097.3,1544.3]	1.39 [1.10, 1.76]
33F	225	7658.2 [6364.1,9215.4]	225	8816.9 [7315.8,10625.9]	0.87 [0.68, 1.12]
Cross-reactive serotype					
15B	224	2084.3 [1700.4,2555.0]	221	1460.7 [1193.3,1788.1]	1.43 [1.07, 1.89]
Non-shared serotype					
15C	223	2478.8 [2021.8, 3039.0]	224	1209.1 [980.6, 1490.9]	2.05 [1.56, 2.70]

a) GMT, GMR, and 95% CI were calculated using a cLDA model. This model used natural log-transformed antibody titers at baseline and at Day 30 postvaccination as response variables and included timepoint, vaccine group, the interaction between timepoint and vaccine group, age category (65-74 years, ≥75 years), and the interaction between timepoint and age category. An unstructured covariance matrix was used to model correlations among repeated measurements.

Table 14. Serotype-specific OPA responder rates at Day 30 after the study vaccination for 8 non-shared serotypes (excluding serotype 15C) (PP population)

Serotype	Capvaxive (N = 225)	PPSV23 (N = 225)	Difference between groups [two-sided 95% CI] ^{a)}
6A	72.8 (134/184)	45.3 (86/190)	27.6 [17.8, 36.9]
15A	59.7 (108/181)	26.0 (44/169)	33.7 [23.6, 43.0]
16F	50.3 (99/197)	11.9 (24/201)	38.3 [29.8, 46.4]
23A	57.6 (83/144)	27.9 (31/111)	29.5 [17.4, 40.6]
23B	82.1 (165/201)	43.7 (87/199)	38.3 [29.3, 46.7]
24F	42.9 (85/198)	16.0 (28/175)	27.1 [18.3, 35.6]
31	70.3 (154/219)	13.1 (28/214)	57.3 [49.3, 64.4]
35B	52.9 (117/221)	6.0 (13/218)	47.0 [39.5, 54.1]

Proportion of participants % (number of applicable participants/number of participants analyzed)

a) The difference between groups and the two-sided 95% CI were calculated using the stratified Miettinen-Nurminen method with age category (65-74 years and ≥75 years) as a stratification factor.

Table 15 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events were assessed as adverse reactions.

Table 15. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 225)	PPSV23 (N = 225)
Local	30.2 (68)	39.1 (88)
Injection site pain	26.2 (59)	36.0 (81)
Injection site erythema	5.8 (13)	10.7 (24)
Injection site swelling	4.0 (9)	7.6 (17)
Systemic	10.7 (24)	14.7 (33)
Fatigue	6.7 (15)	11.1 (25)
Headache	3.6 (8)	2.2 (5)
Myalgia	2.7 (6)	2.2 (5)
Pyrexia ^{a)}	0	0.4 (1)

Incidence % (n), MedDRA version 26.1

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events occurred in 38.2% (86 of 225) of participants in the Capvaxive group and 44.4% (100 of 225) of participants in the PPSV23 group. Adverse events reported by $\geq 5\%$ of participants in either group were injection site pain (60 participants in the Capvaxive group and 81 participants in the PPSV23 group), injection site erythema (19 and 24 participants, respectively), fatigue (15 and 25 participants, respectively), and injection site swelling (14 and 17 participants, respectively).

Within 30 days after the study vaccination, adverse reactions occurred in 35.6% (80 of 225) of participants in the Capvaxive group and 43.1% (97 of 225) of participants in the PPSV23 group. All of the local adverse events were assessed as adverse reactions. A systemic adverse reaction reported by $\geq 5\%$ of participants in either group was fatigue (15 participants in the Capvaxive group, 23 participants in the PPSV23 group).

Neither deaths nor adverse events leading to study discontinuation occurred.

During the study period, a serious adverse event occurred in 1 participant in the Capvaxive group (lacunar infarction), but a causal relationship to Capvaxive was ruled out.

7.3.2 Foreign phase III study (CTD 5.3.5.1.4, Study 003, study period, July 2022 to May 2023)

A randomized, double-blind,⁴⁾ parallel-group study was conducted at 112 study sites in 11 countries or regions¹¹⁾ to investigate the safety and immunogenicity of Capvaxive in pneumococcal vaccine-naïve adults aged ≥ 18 years (including those with medically stable underlying diseases) (target sample size,

¹¹⁾ Australia, Belgium, Chile, Germany, New Zealand, Puerto Rico, South Korea, Sweden, Taiwan, Turkey, and US

2,600 participants; 2,300¹²⁾ in Cohort 1 [≥ 50 years] [1,150 in the Capvaxive group and 1,150 in the PCV20 group] and 300¹³⁾ in Cohort 2 [18-49 years] [200 in the Capvaxive group and 100 in the PCV20 group]).

A single dose of Capvaxive⁹⁾ or PCV20 0.5 mL was intramuscularly administered.

Cohort 1

Of the 2,362 randomized participants¹⁴⁾ (1,181 in the Capvaxive group and 1,181 in the PCV20 group), 2,356 participants (1,179 and 1,177 participants, respectively) received the study vaccine, excluding 6 participants (2 and 4 participants, respectively). Of those who received the study vaccine, 2,352 participants (1,177 and 1,175 participants, respectively) were included in the safety analysis set, excluding 4 participants¹⁵⁾ (2 participants from each group). Among participants who received the study vaccine, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the PP population. All participants who received the study vaccine were included in the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoints were “serotype-specific OPA GMTs at Day 30 after the study vaccination” and “serotype-specific OPA responder rate at Day 30 after the study vaccination.” The following criteria (i), (ii), and (iii) were specified for demonstration of non-inferiority ([i]) and superiority ([ii] and [iii]) of Capvaxive to PCV20:

- (i) For 10 shared serotypes, the lower bound of the 95% CI of the ratio of serotype-specific OPA GMT at Day 30 after the study vaccination in the Capvaxive group to that in the PCV20 group (GMR) exceeds 0.5.
- (ii) For 11 non-shared serotypes, the lower bound of the 95% CI of serotype-specific OPA GMR at Day 30 after the study vaccination exceeds 2.0.

¹²⁾ In view of results from a foreign phase I/II study (Study 001), the sample size of 1,035 participants per group was calculated to simultaneously demonstrate all the following (i) to (iii) in terms of OPA GMT and OPA responder rate, the primary endpoints, by tests at a one-sided significance level of 0.025 with a power of approximately 90% on hypotheses listed below: (i) Non-inferiority of Capvaxive to PCV20 for 10 shared serotypes (non-inferiority margin of 0.5 for OPA GMR); (ii) superiority of Capvaxive to PCV20 for 11 non-shared serotypes (superiority margin of 2.0 for OPA GMR); and (iii) superiority of Capvaxive to PCV20 for 11 non-shared serotypes (superiority margin of 10% for the difference in OPA responder rate between Capvaxive and PCV20). On the assumption that 10% of participants would be excluded from the evaluable population, the target sample size of 1,150 participants per group was specified.

- For (i), GMR (Capvaxive/PCV20) is 1.0 for 4 of 10 shared serotypes and 0.68 for the remaining 6 shared serotypes. The standard deviation of natural log-transformed antibody titers ranges from 1.06 to 1.64 in the Capvaxive group and from 1.31 to 2.22 in the PCV20 group for 4 serotypes, and from 1.27 to 1.73 in the Capvaxive group and from 1.69 to 2.13 in the PCV20 group for the remaining 6 serotypes.
- For (ii), GMR (Capvaxive/PCV20) is 2.0 for non-shared serotype 15C of 11 non-shared serotypes and 6.0 for the remaining 10 non-shared serotypes. The standard deviation of natural log-transformed antibody titers ranges from 1.25 to 1.95 for 11 non-shared serotypes in both the Capvaxive and PCV20 groups.
- For (iii), the OPA responder rate is 80% in the Capvaxive group and at most 50% in the PCV20 group for each of the 11 non-shared serotypes.

¹³⁾ In view of results from a foreign phase I/II study (Study 001), the target sample size of 200 participants in the Capvaxive group in Cohort 2 was established to demonstrate the following in terms of OPA GMT, the primary endpoint, by a test at a one-sided significance level of 0.025 with a power of $>90\%$ on hypotheses listed below: Non-inferiority of the Capvaxive group in Cohort 2 (adults aged 18-49 years) to the Capvaxive group in Cohort 1 (adults aged 50-64 years) for 10 shared serotypes and 11 non-shared serotypes (non-inferiority margin of 0.5 for OPA GMR).

- Ten percent of participants would be excluded from the evaluable population. Adults aged 50 to 64 years constitute 50% of participants in Cohort 1.
- For the cohort comparison, serotype-specific OPA GMR (Cohort 2/Cohort 1) is 1.0, and the standard deviation of natural log-transformed antibody titers ranges from 0.66 to 1.73 in the Capvaxive group (adults aged 18-49 years) in Cohort 2 and from 1.06 to 1.92 in the Capvaxive group (adults aged 50-64 years) in Cohort 1.

¹⁴⁾ Randomization was performed using the age category (50-64 years, 65-74 years, 75-84 years, or ≥ 85 years) as a stratification factor.

¹⁵⁾ Two participants were randomized twice (counted as 4 participants under separate allocation numbers) and received PCV20 for the first participation and Capvaxive for the second one. They completed the study for the first participation and discontinued the study for the second one.

- (iii) For 11 non-shared serotypes, the lower bound of the 95% CI of difference in serotype-specific OPA responder rate (%) at Day 30 after the study vaccination between the Capvaxive group and PCV20 group exceeds 10%.

For immunogenicity, Table 16 shows serotype-specific OPA GMTs at Day 30 after the study vaccination in the Capvaxive group and PCV20 group. For (i), non-inferiority was demonstrated for all of the 10 shared serotypes, and for (ii), the superiority criterion was met for 10 non-shared serotypes excluding the serotype 15C. Table 17 shows serotype-specific OPA responder rates at Day 30 after the study vaccination in the Capvaxive group and PCV20 group. For (iii), the superiority criterion was met for 10 non-shared serotypes excluding the serotype 15C.

Table 16. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (N = 1,179)		PCV20 (N = 1,177)		GMR [two-sided 95% CI] ^{a)}
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	
10 shared serotypes					
3	1,154	274.0 [254.7, 294.7]	1,161	176.7 [164.2, 190.2]	1.55 [1.40, 1.72]
6A	1,148	2302.0 [2105.1, 2517.4]	1,153	2972.5 [2716.7, 3252.4]	0.77 [0.68, 0.88]
7F	1,152	3637.4 [3363.0, 3934.2]	1,158	3429.9 [3171.1, 3709.9]	1.06 [0.95, 1.18]
8	1,155	2501.3 [2330.6, 2684.5]	1,158	1811.1 [1686.4, 1945.0]	1.38 [1.25, 1.53]
10A	1,161	3893.4 [3609.1, 4200.0]	1,159	4678.0 [4328.6, 5055.5]	0.83 [0.75, 0.93]
11A	1,145	3232.6 [2995.3, 3488.6]	1,150	2092.8 [1939.2, 2258.5]	1.54 [1.39, 1.72]
12F	1,160	2641.2 [2403.9, 2901.9]	1,161	2499.6 [2272.8, 2749.1]	1.06 [0.92, 1.21]
19A	1,159	2136.1 [1990.3, 2292.6]	1,162	2817.8 [2623.0, 3027.1]	0.76 [0.69, 0.84]
22F	1,147	3874.5 [3562.5, 4213.9]	1,154	4770.1 [4382.4, 5192.1]	0.81 [0.72, 0.92]
33F	1,154	13558.9 [12347.4, 14889.2]	1,157	11742.1 [10691.0, 12896.5]	1.15 [1.01, 1.32]
11 non-shared serotypes					
9N	1,147	7470.7 [6929.9, 8053.6]	1,150	1640.4 [1524.7, 1765.0]	4.55 [4.12, 5.04]
15A	1,107	5237.2 [4789.7, 5726.4]	1,102	1589.0 [1450.8, 1740.3]	3.30 [2.91, 3.74]
15C	1,153	4216.2 [3810.2, 4665.5]	1,158	2072.3 [1872.3, 2293.6]	2.03 [1.77, 2.34]
16F	1,151	4868.2 [4489.7, 5278.7]	1,153	846.3 [781.6, 916.4]	5.75 [5.16, 6.41]
17F	1,148	7764.9 [7053.9, 8547.5]	1,156	460.4 [419.7, 505.1]	16.86 [14.90, 19.09]
20A	1,161	6099.2 [5610.8, 6630.0]	1,155	631.1 [580.8, 685.7]	9.66 [8.66, 10.79]
23A	1,132	3737.2 [3319.3, 4207.7]	1,104	461.5 [408.2, 521.8]	8.10 [6.86, 9.55]
23B	1,160	1082.5 [954.4, 1227.8]	1,160	107.3 [94.6, 121.8]	10.09 [8.48, 12.00]
24F	1,153	2728.6 [2462.1, 3024.0]	1,130	70.5 [63.4, 78.4]	38.71 [33.87, 44.25]
31	1,153	3132.5 [2800.6, 3503.8]	1,154	144.4 [129.4, 161.2]	21.69 [18.68, 25.18]
35B	1,153	8527.8 [7919.5, 9182.8]	1,159	1383.0 [1286.7, 1486.6]	6.17 [5.59, 6.80]

a) GMT, GMR, and 95% CI were calculated using a cLDA model. This model used natural log-transformed antibody titers at baseline and at Day 30 postvaccination as response variables and included timepoint, vaccine group, the interaction between timepoint and vaccine group, age category (50-64 years, 65-74 years, ≥75 years), and the interaction between timepoint and age category. An unstructured covariance matrix was used to model correlations among repeated measurements.

Table 17. Serotype-specific OPA responder rates from baseline to Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (N = 1,179)	PCV20 (N = 1,177)	Difference between groups [two-sided 95% CI] ^{a)}
11 non-shared serotypes			
9N	64.7 (595/920)	19.9 (195/978)	44.7 [40.7, 48.6]
15A	66.7 (462/693)	35.8 (253/706)	30.9 [25.8, 35.8]
15C	83.4 (794/952)	74.2 (695/937)	9.2 [5.6, 12.9]
16F	71.9 (654/910)	20.8 (200/961)	51.1 [47.1, 54.9]
17F	75.8 (653/862)	9.5 (90/952)	66.3 [62.8, 69.6]
20A	67.3 (675/1,003)	9.6 (97/1,011)	57.7 [54.2, 61.1]
23A	78.9 (598/758)	36.8 (270/734)	42.2 [37.6, 46.6]
23B	85.5 (873/1,021)	49.6 (506/1,021)	35.9 [32.1, 39.6]
24F	80.5 (745/925)	6.3 (55/872)	74.2 [71.1, 77.1]
31	76.5 (698/912)	17.9 (171/954)	58.6 [54.8, 62.1]
35B	60.0 (550/917)	6.8 (67/988)	53.2 [49.6, 56.6]

Proportion of participants % (number of applicable participants/number of participants analyzed)

a) The difference between groups and the two-sided 95% CI were calculated using the stratified Miettinen-Nurminen method with age category (50-64 years, 65-74 years, and ≥75 years) as a stratification factor.

Table 18 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions.

Table 18. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 1,177)	PCV20 (N = 1,175)
Local	41.4 (487)	53.6 (630)
Injection site pain	39.4 (464)	51.7 (607)
Injection site swelling	6.0 (71)	8.3 (98)
Injection site erythema	5.4 (64)	6.3 (74)
Systemic	28.4 (334)	27.5 (323)
Fatigue	20.1 (237)	19.6 (230)
Headache	11.5 (135)	12.9 (152)
Myalgia	5.9 (70)	6.7 (79)
Pyrexia ^{a)}	1.3 (15)	1.3 (15)

Incidence % (n), MedDRA version 26.0

a) Oral temperature ≥38.0°C

Within 30 days after the study vaccination, adverse events occurred in 58.2% (685 of 1,177) of participants in the Capvaxive group and 66.2% (778 of 1,175) of participants in the PCV20 group. Adverse events reported by ≥5% of participants in either group were injection site pain (471 participants in the Capvaxive group and 608 participants in the PCV20 group), fatigue (240 and 235 participants, respectively), headache (162 and 174 participants, respectively), injection site erythema (82 and 86 participants, respectively), injection site swelling (79 and 103 participants, respectively), and myalgia (75 and 82 participants, respectively).

Within 30 days after the study vaccination, adverse reactions occurred in 51.7% (609 of 1,177) of participants in the Capvaxive group and 60.9% (715 of 1,175) of participants in the PCV20 group. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions, and systemic adverse reactions reported by ≥5% of participants in either group were fatigue (211 participants in the Capvaxive group and 212 participants in the PCV20 group), headache (125 and 137 participants, respectively), and myalgia (68 and 74 participants, respectively).

Adverse events leading to death occurred in 4 participants in the Capvaxive group (sepsis,¹⁶⁾ cerebrovascular accident,¹⁷⁾ myocardial infarction,¹⁸⁾ hepatic cirrhosis,¹⁹⁾ and hepatic encephalopathy¹⁹⁾ in 1 participant each; some participants had multiple events) and in 2 participants in the PCV20 group (cardiac arrest²⁰⁾ and abdominal abscess²¹⁾ in 1 participant each), but a causal relationship to the study vaccine was ruled out for all of them.

During the study period, serious adverse events occurred in 19 participants in the Capvaxive group (sepsis and cerebrovascular accident in 2 participants each, cardiac arrest, myocardial infarction, abdominal pain upper, duodenal ulcer perforation, inguinal hernia, oral mucosa erosion, hepatic cirrhosis, hepatic necrosis, subcapsular hepatic haematoma, abdominal wall abscess, appendicitis, diverticulitis, peritonitis, pneumonia aspiration, septic shock, upper limb fracture, diabetes mellitus inadequate control, hyponatraemia, osteoarthritis, invasive ductal breast carcinoma, rectal adenocarcinoma, dizziness, hepatic encephalopathy, device occlusion, alcoholism, delirium tremens, nephrolithiasis, acute respiratory failure, and dyspnoea in 1 participant each; some participants had multiple events) and in 24 participants in the PCV20 group (myocardial infarction in 4 participants, cardiac arrest, coronary artery embolism, vertigo, abdominal pain, colitis, small intestinal obstruction, non-cardiac chest pain, drug hypersensitivity, abdominal abscess, encephalitis viral, gastroenteritis, pneumonia, brain contusion, hip fracture, lumbar spinal stenosis, prostate cancer, encephalopathy, ischaemic stroke, metabolic encephalopathy, radial nerve palsy, alcohol withdrawal syndrome, acute kidney injury, and nephrolithiasis in 1 participant each; some participants had multiple events), but a causal relationship to the study vaccine was ruled out for all of them.

No adverse events leading to study discontinuation occurred.

Cohort 2

Of the 301 randomized participants (201 in the Capvaxive group, 100 in the PCV20 group), 300 participants (200 in the Capvaxive group, 100 in the PCV20 group) received the study vaccine and were included in the safety analysis set, excluding 1 participant in the Capvaxive group. Among all randomized participants, those without protocol deviations that could have a significant impact on

¹⁶⁾ 71-year-old woman. On Day 25 after the study vaccination (Capvaxive), she underwent a liver biopsy. At that time, she was found to have subcapsular liver haematoma and thus underwent hepatic artery embolization on the same day. On Day 27, she had septic shock and thus was hospitalized. On the following day, she had cardiac arrest but was resuscitated. Echocardiography revealed aortic stenosis. On Day 36, computed tomography (CT) revealed hepatic necrosis and perihepatic fluid retention, and culture of the drained perihepatic fluid grew *E. hirae*, *K. variicola*, and *E. coli*. On Day 39, a drain catheter was placed. Her condition improved, and she was discharged on Day 61. On Day 86, she had septic shock again and thus was hospitalized. Six days later, she underwent drainage and catheterization again. On Day 111, she was discharged but died 15 days later. A causal relationship to the study vaccine was ruled out.

¹⁷⁾ 51-year-old woman. On Day 43 after the study vaccination (Capvaxive), she died of cerebrovascular accident. A causal relationship to the study vaccine was ruled out.

¹⁸⁾ 51-year-old woman. On Day 178 after the study vaccination (Capvaxive), she died of myocardial infarction. A causal relationship to the study vaccine was ruled out.

¹⁹⁾ 71-year-old man. On Day 19 after the study vaccination (Capvaxive), he experienced dizziness, confusion, and fall and thus was hospitalized. Spinal and head CT revealed no abnormalities, but abdominal CT revealed ascites. He was discharged 2 days later, but on the following day, he was hospitalized again owing to confusion. Abdominal ultrasonography revealed splenomegaly and ascites increased, leading to diagnoses of hepatic cirrhosis and hepatic encephalopathy. On Day 85, he was discharged. However, his condition did not improve thereafter, and he died on Day 128. A causal relationship to the study vaccine was ruled out.

²⁰⁾ 71-year-old man. He had a medical history of cardiac pacemaker insertion. On Day 9 after the study vaccination (PCV20), he died of cardiac arrest. A causal relationship to the study vaccine was ruled out.

²¹⁾ 61-year-old woman. She had a medical history of gastroenteritis and *H. pylori* infection. On Day 13 after the study vaccination (PCV20), she was hospitalized owing to nausea lasting almost 1 and half months, vomiting, abdominal pain, and weight decreased. CT led to a diagnosis of abdominal abscess. On Day 14, a percutaneous drainage catheter was placed in the peritoneal cavity. Three days later, laparoscopic surgery was performed. Then, antimicrobial treatment was continued, but on Day 62, she died. A causal relationship to the study vaccine was ruled out.

immunogenicity evaluation were defined as the PP population. All participants who received the study vaccine were included in the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoint was “serotype-specific OPA GMTs at Day 30 after the study vaccination.” The criterion for immunobridging for adults aged 18 to 49 years with those aged 50 to 64 years was predefined as follows: The lower bound of the 95% CI of the ratio of serotype-specific OPA GMT at Day 30 after the study vaccination for all 21 serotypes in adults aged 18 to 49 years in the Capvaxive group (Cohort 2) to that in adults aged 50 to 64 years in the Capvaxive group (Cohort 1) (GMR) exceeds 0.5. Table 19 shows serotype-specific OPA GMTs at Day 30 after the study vaccination in adults aged 18 to 49 years and those aged 50 to 64 years in the Capvaxive group. For all serotypes, the criterion for immunobridging was met.

Table 19. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (18-49 years) (N = 200)		Capvaxive (50-64 years) (N = 589)		GMR [two-sided 95% CI] ^{a)}
	No. of participants	GMT ^{a)}	No. of participants	GMT ^{a)}	
3	194	308.6 [260.4, 365.8]	572	282.7 [256.7, 311.3]	1.09 [0.90, 1.33]
6A	196	5289.6 [4289.2, 6523.4]	569	2572.9 [2281.7, 2901.3]	2.06 [1.61, 2.62]
7F	198	6447.2 [5427.2, 7659.0]	571	4278.8 [3871.1, 4729.5]	1.51 [1.23, 1.84]
8	197	4516.0 [3873.1, 5265.7]	571	3004.7 [2751.6, 3281.0]	1.50 [1.26, 1.79]
9N	197	17283.2 [14346.2, 20821.5]	570	8791.4 [7934.3, 9741.0]	1.97 [1.59, 2.43]
10A	197	6808.1 [5661.8, 8186.3]	575	4382.6 [3942.1, 4872.4]	1.55 [1.26, 1.92]
11A	196	5871.6 [4909.1, 7022.9]	564	3785.8 [3413.2, 4199.0]	1.55 [1.26, 1.91]
12F	196	6150.4 [5046.0, 7496.4]	574	3561.2 [3177.3, 3991.4]	1.73 [1.37, 2.17]
15A	184	11319.2 [9418.9, 13602.9]	550	5901.2 [5321.4, 6544.2]	1.92 [1.55, 2.37]
15C	195	10194.0 [8033.0, 12936.4]	570	5708.0 [4986.7, 6533.6]	1.79 [1.36, 2.35]
16F	193	8877.0 [7418.6, 10622.2]	571	5720.0 [5167.3, 6331.9]	1.55 [1.26, 1.91]
17F	194	16070.6 [13078.4, 19747.3]	568	10068.0 [8980.3, 11287.5]	1.60 [1.26, 2.02]
19A	198	2773.2 [2368.9, 3246.5]	574	2374.6 [2166.9, 2602.3]	1.17 [0.97, 1.40]
20A	197	13150.0 [10799.8, 16011.7]	575	7562.7 [6763.6, 8456.1]	1.74 [1.39, 2.18]
22F	198	9299.6 [7649.0, 11306.5]	568	4683.6 [4185.6, 5240.9]	1.99 [1.58, 2.49]
23A	192	8848.7 [7026.8, 11143.0]	561	4739.5 [4147.0, 5416.5]	1.87 [1.43, 2.44]
23B	198	2140.1 [1643.8, 2786.1]	575	1420.9 [1220.6, 1654.1]	1.51 [1.11, 2.04]
24F	197	4137.6 [3451.9, 4959.4]	570	3047.2 [2744.4, 3383.5]	1.36 [1.10, 1.67]
31	195	8005.6 [6442.7, 9947.6]	570	3820.7 [3373.5, 4327.2]	2.10 [1.63, 2.69]
33F	197	34805.5 [27692.5, 43745.6]	570	17607.4 [15448.4, 20068.3]	1.98 [1.52, 2.57]
35B	198	13933.4 [11745.5, 16528.8]	573	9053.9 [8215.3, 9978.1]	1.54 [1.26, 1.87]

a) GMT, GMR, and 95% CI were calculated using a longitudinal data analysis (LDA) model. This model used natural log-transformed antibody titers at baseline and at Day 30 postvaccination as response variables and included timepoint, age category (cohort), and interaction between timepoint and age category (cohort). An unstructured covariance matrix was used to model correlations among repeated measurements.

Table 20 shows incidences of local and systemic solicited adverse events in the Capvaxive group and PCV20 group within 5 days after the study vaccination. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions.

Table 20. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 200)	PCV20 (N = 100)
Local	72.0 (144)	75.0 (75)
Injection site pain	71.5 (143)	74.0 (74)
Injection site erythema	15.5 (31)	13.0 (13)
Injection site swelling	14.0 (28)	14.0 (14)
Systemic	53.5 (107)	44.0 (44)
Fatigue	40.5 (81)	34.0 (34)
Headache	29.5 (59)	24.0 (24)
Myalgia	16.5 (33)	14.0 (14)
Pyrexia ^{a)}	3.5 (7)	1.0 (1)

Incidence % (n), MedDRA version 26.0

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events occurred in 82.0% (164 of 200) of participants in the Capvaxive group and 79.0% (79 of 100) of participants in the PCV20 group. Adverse events reported by $\geq 5\%$ of participants in either group were injection site pain (143 participants in the Capvaxive group and 74 participants in the PCV20 group), fatigue (81 and 34 participants, respectively), headache (59 and 26 participants, respectively), myalgia (33 and 14 participants, respectively), injection site erythema (32 and 13 participants, respectively), and injection site swelling (28 and 14 participants, respectively).

Within 30 days after the study vaccination, adverse reactions occurred in 79.5% (159 of 200) of participants in the Capvaxive group and 78.0% (78 of 100) of participants in the PCV20 group. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions, and systemic adverse reactions reported by $\geq 5\%$ of participants in either group were fatigue (77 participants in the Capvaxive group and 30 participants in the PCV20 group), headache (54 and 23 participants, respectively), and myalgia (33 and 12 participants, respectively).

Neither deaths nor adverse events leading to study discontinuation occurred.

During the study period, serious adverse events occurred in 1 participant in the Capvaxive group (tooth abscess in 1 participant) and 3 participants in the PCV20 group (jejunal perforation, cellulitis, and lower limb fracture in 1 participant each), but a causal relationship to the study vaccine was ruled out for all of them.

7.3.3 Global phase III study (CTD 5.3.5.1.7, Study 006, study period, July 2022 to May 2023)

A randomized, double-blind,⁴⁾ parallel-group study (Cohorts 1 and 2) and an open-label single-arm study (Cohort 3) were conducted at 51 study sites in 9 countries or regions²²⁾ to investigate the safety and immunogenicity of Capvaxive in adults aged ≥ 50 years with prior pneumococcal vaccination²³⁾ (including those with medically stable underlying diseases) (target sample size, 700 participants²⁴⁾; 300 participants in Cohort 1 [200 in the Capvaxive group, 100 in the PCV15 group], 300 participants in

²²⁾ Canada, France, Israel, Italy, Japan, South Korea, Spain, Taiwan, and US

²³⁾ Cohort 1 included adults with prior PPSV23 vaccination, Cohort 2 included those with prior PCV13 vaccination, and Cohort 3 included those with prior PCV13 + PPSV23, PCV15 + PPSV23, PPSV23 + PCV13, PCV15, or PCV20 vaccination. In all cohorts, adults who had received a pneumococcal vaccine at least 1 year before enrollment were considered eligible.

²⁴⁾ In this study, immunogenicity and safety were planned to be evaluated using descriptive statistics, and thus no statistical tests of hypotheses were planned. Accordingly, the target sample size was not established based on statistical hypotheses.

Cohort 2 [200 in the Capvaxive group, 100 in the PPSV23 group, 100 participants in the Capvaxive group in Cohort 3).

Cohort 1

A single dose of Capvaxive⁹⁾ or PCV15 0.5 mL was intramuscularly administered.

Of the 350 randomized participants²⁵⁾ (231 in the Capvaxive group and 119 in the PCV15 group), 348 participants (229 and 119 participants, respectively) received the study vaccine, excluding 2 participants in the Capvaxive group. Of those who received the study vaccine, 347 participants (230 and 117 participants, respectively) were included in the safety analysis set, excluding 1 participant who received PPSV23 among 2 participants²⁶⁾ in the PCV15 group who received the wrong study vaccine. Among all randomized participants, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the PP population. All participants who received the study vaccine were included in the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoint was “serotype-specific OPA GMTs at Day 30 after the study vaccination,” and the results are as shown in Table 21.

Table 21. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (N = 229)		PCV15 (N = 119)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
6 shared serotypes				
3	197	262.1 [224.0, 306.8]	103	226.3 [182.0, 281.4]
6A	191	1653.5 [1347.2, 2029.4]	94	2076.1 [1571.4, 2742.8]
7F	209	2184.4 [1891.4, 2522.8]	110	1750.3 [1404.7, 2181.0]
19A	204	1513.8 [1318.4, 1738.1]	109	2022.9 [1634.1, 2504.3]
22F	206	1983.8 [1698.3, 2317.4]	108	1595.6 [1227.1, 2074.6]
33F	188	4311.9 [3625.1, 5128.9]	99	3397.2 [2665.3, 4330.0]
15 non-shared serotypes				
8	208	1273.0 [1115.1, 1453.3]	113	345.8 [250.5, 477.5]
9N	191	3805.1 [3324.0, 4356.0]	111	2176.5 [1809.6, 2617.9]
10A	209	1986.2 [1637.7, 2408.9]	112	467.5 [337.0, 648.5]
11A	197	1998.5 [1696.9, 2353.8]	100	335.6 [228.9, 491.8]
12F	212	981.8 [782.4, 1232.1]	114	80.5 [54.0, 120.1]
15A	175	4184.9 [3548.3, 4935.6]	93	877.2 [616.2, 1248.7]
15C	206	2307.8 [1878.4, 2835.4]	110	539.6 [371.1, 784.6]
16F	187	3060.5 [2633.8, 3556.3]	107	392.3 [301.3, 510.8]
17F	194	3599.8 [3134.5, 4134.3]	108	939.6 [693.7, 1272.6]
20A	195	2847.4 [2433.3, 3331.8]	110	1058.9 [829.9, 1351.1]
23A	202	2363.9 [1857.4, 3008.5]	91	310.2 [202.1, 476.0]
23B	197	673.2 [517.1, 876.4]	110	153.0 [98.7, 237.1]
24F	201	1822.6 [1411.6, 2353.3]	97	106.6 [69.7, 162.9]
31	194	3018.4 [2473.6, 3683.3]	108	113.2 [74.5, 172.1]
35B	194	6703.1 [5732.7, 7837.8]	107	1019.1 [739.9, 1403.7]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

²⁵⁾ Randomization was performed using the age category (50-64 years or ≥65 years) and period from the last pneumococcal vaccination (1-4 years, 5-9 years, or ≥10 years) as stratification factors.

²⁶⁾ Instead of PCV15, Capvaxive or PPSV23 was mistakenly administered (to 1 participant each).

Table 22 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions.

Table 22. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 230)	PCV15 (N = 117)
Local	40.0 (92)	47.9 (56)
Injection site pain	35.7 (82)	43.6 (51)
Injection site swelling	8.3 (19)	8.5 (10)
Injection site erythema	7.4 (17)	7.7 (9)
Systemic	20.9 (48)	21.4 (25)
Fatigue	14.3 (33)	17.1 (20)
Myalgia	7.4 (17)	2.6 (3)
Headache	7.0 (16)	9.4 (11)
Pyrexia ^{a)}	1.7 (4)	2.6 (3)

Incidence % (n), MedDRA version 26.0

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events occurred in 51.3% (118 of 230) of participants in the Capvaxive group and 64.1% (75 of 117) of participants in the PCV15 group. Adverse events reported by $\geq 5\%$ of participants in either group were injection site pain (82 participants in the Capvaxive group and 51 participants in the PCV15 group), fatigue (33 and 20 participants, respectively), injection site swelling (20 and 10 participants, respectively), injection site erythema (19 and 9 participants, respectively), headache (17 and 11 participants, respectively), and myalgia (17 and 5 participants, respectively).

Within 30 days after the study vaccination, adverse reactions occurred in 46.5% (107 of 230) of participants in the Capvaxive group and 56.4% (66 of 117) of participants in the PCV15 group. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions, and systemic adverse reactions reported by $\geq 5\%$ of participants in either group were fatigue (31 participants in the Capvaxive group and 20 participants in the PCV15 group), myalgia (17 and 4 participants, respectively), and headache (16 and 11 participants, respectively).

Neither deaths nor adverse events leading to study discontinuation occurred.

During the study period, serious adverse events occurred in 2 participants in the Capvaxive group (cardiac failure congestive and injection site cellulitis in 1 participant each) and 4 participants in the PCV15 group (cardiac failure, myocardial ischaemia, aortoenteric fistula, Mallory-Weiss syndrome, small intestinal perforation, pneumonia, and hypotension in 1 participant each; some participants had multiple events). A causal relationship to Capvaxive could not be ruled out for injection site cellulitis in the Capvaxive group, but the event resolved.

Cohort 2

A single dose of Capvaxive⁹⁾ or PPSV23 0.5 mL was intramuscularly administered.

Of the 261 randomized participants²⁵⁾ (176 in the Capvaxive group, 85 in the PPSV23 group), 259 participants (174 in the Capvaxive group, 85 in the PPSV23 group) received the study vaccine and were

included in the safety analysis set, excluding 2 participants in the Capvaxive group. Among all randomized participants, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the PP population. All participants who received the study vaccine were included in the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoint was “serotype-specific OPA GMTs at Day 30 after the study vaccination,” and the results are as shown in Table 23.

Table 23. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (N = 174)		PPSV23 (N = 85)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
12 shared serotypes				
3	149	391.1 [332.8, 459.6]	75	583.1 [453.5, 749.6]
7F	150	3129.8 [2609.9, 3753.3]	70	4057.0 [3211.2, 5125.6]
8	161	2320.1 [1987.3, 2708.7]	75	2723.2 [2197.4, 3374.8]
9N	143	7214.4 [6062.9, 8584.6]	58	6482.5 [4908.9, 8560.7]
10A	155	3976.8 [3360.7, 4705.8]	73	1797.6 [1136.2, 2843.9]
11A	142	2846.6 [2411.0, 3360.8]	71	1736.6 [1367.1, 2206.0]
12F	160	2552.6 [2120.5, 3072.9]	73	1402.5 [912.2, 2156.4]
17F	125	5963.8 [5036.6, 7061.7]	67	4367.3 [3372.5, 5655.7]
19A	158	2528.9 [2201.7, 2904.9]	74	3241.5 [2646.0, 3971.0]
20A	138	6005.5 [4919.8, 7330.8]	72	3393.9 [2536.9, 4540.5]
22F	143	4389.2 [3541.1, 5440.3]	71	2524.0 [1834.5, 3472.5]
33F	131	8162.9 [6407.2, 10399.7]	59	8761.9 [6157.4, 12468.1]
9 non-shared serotypes				
6A	152	3624.0 [3099.2, 4237.7]	74	1812.3 [1226.6, 2677.6]
15A	134	6185.2 [5179.3, 7386.6]	63	1668.2 [1234.4, 2254.5]
15C	152	4334.4 [3563.8, 5271.5]	72	1470.4 [978.6, 2209.3]
16F	146	4626.5 [3861.8, 5542.6]	74	832.8 [604.3, 1147.6]
23A	156	4253.4 [3417.6, 5293.5]	60	433.6 [247.5, 759.5]
23B	160	1530.7 [1196.5, 1958.3]	75	203.9 [127.6, 325.6]
24F	151	2746.1 [2257.9, 3339.9]	63	48.5 [28.6, 82.1]
31	146	4413.5 [3530.2, 5517.7]	68	171.8 [99.9, 295.6]
35B	148	8143.5 [6761.4, 9808.1]	76	1527.7 [1169.5, 1995.5]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

Table 24 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions.

Table 24. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 174)	PPSV23 (N = 85)
Local	43.1 (75)	54.1 (46)
Injection site pain	41.4 (72)	47.1 (40)
Injection site erythema	7.5 (13)	9.4 (8)
Injection site swelling	4.6 (8)	16.5 (14)
Systemic	25.9 (45)	23.5 (20)
Fatigue	19.0 (33)	12.9 (11)
Headache	10.3 (18)	11.8 (10)
Myalgia	9.8 (17)	9.4 (8)
Pyrexia ^{a)}	2.9 (5)	1.2 (1)

Incidence % (n), MedDRA version 26.0

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events occurred in 52.9% (92 of 174) of participants in the Capvaxive group and 65.9% (56 of 85) of participants in the PPSV23 group. Adverse events reported by $\geq 5\%$ of participants in either group were injection site pain (72 participants in the Capvaxive group and 40 participants in the PPSV23 group), fatigue (33 and 12 participants, respectively), headache (18 and 10 participants, respectively), myalgia (17 and 9 participants, respectively), injection site erythema (14 and 8 participants, respectively), and injection site swelling (8 and 14 participants, respectively).

Within 30 days after the study vaccination, adverse reactions occurred in 50.0% (87 of 174) of participants in the Capvaxive group and 61.2% (52 of 85) of participants in the PPSV23 group. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions, and systemic adverse reactions reported by $\geq 5\%$ of participants in either group were fatigue (32 participants in the Capvaxive group and 12 participants in the PPSV23 group), headache (18 and 10 participants, respectively), and myalgia (17 and 8 participants, respectively).

Neither deaths nor adverse events leading to study discontinuation occurred.

During the study period, serious adverse events occurred in 2 participants in the Capvaxive group (anal fissure and chronic obstructive pulmonary disease in 1 participant each) and 3 participants in the PPSV23 group (cholangitis, ischaemic stroke, and chronic obstructive pulmonary disease in 1 participant each), but a causal relationship to the study vaccine was ruled out for all of them.

Cohort 3

A single dose of Capvaxive⁹⁾ 0.5 mL was intramuscularly administered.

Of 106 participants enrolled, 105 participants received the study vaccine, and all vaccinated participants were included in the safety analysis set. Among enrolled participants, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the PP population. All participants who received the study vaccine were included in the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoint was “serotype-specific OPA GMTs at Day 30 after the study vaccination,” and the results are as shown in Table 25.

Table 25. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive (N = 105)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
3	85	318.3 [250.0, 405.3]
6A	93	2097.3 [1693.4, 2597.6]
7F	96	2051.3 [1630.2, 2581.0]
8	98	1486.8 [1230.5, 1796.6]
9N	90	4054.5 [3389.4, 4850.2]
10A	96	2564.0 [1959.1, 3355.6]
11A	87	2373.0 [1905.4, 2955.4]
12F	99	1235.3 [948.3, 1609.2]
15A	86	4328.6 [3378.7, 5545.7]
15C	89	2191.9 [1573.2, 3053.9]
16F	89	2477.0 [1887.2, 3251.2]
17F	82	3836.7 [3063.4, 4805.1]
19A	93	1533.8 [1272.4, 1848.9]
20A	88	2433.4 [1880.5, 3148.9]
22F	99	1913.5 [1453.5, 2519.0]
23A	86	3967.2 [2764.8, 5692.7]
23B	97	844.0 [608.2, 1171.4]
24F	90	2041.5 [1500.8, 2777.1]
31	90	3285.5 [2485.0, 4343.8]
33F	88	4654.3 [3532.1, 6133.1]
35B	90	5836.8 [4693.6, 7258.6]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

Table 26 shows incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions.

Table 26. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	Capvaxive (N = 105)
Local	43.8 (46)
Injection site pain	43.8 (46)
Injection site swelling	10.5 (11)
Injection site erythema	7.6 (8)
Systemic	24.8 (26)
Fatigue	21.9 (23)
Headache	8.6 (9)
Myalgia	8.6 (9)
Pyrexia ^{a)}	0

Incidence % (n), MedDRA version 26.0

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Within 30 days after the study vaccination, adverse events occurred in 52.4% (55 of 105) of participants in the Capvaxive group. Adverse events reported by $\geq 5\%$ of participants were injection site pain (46 participants), fatigue (23 participants), injection site swelling (11 participants), myalgia (9 participants), headache (9 participants), and injection site erythema (8 participants).

Within 30 days after the study vaccination, adverse reactions occurred in 48.6% (51 of 105) of participants in the Capvaxive group. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions, and systemic adverse reactions reported by $\geq 5\%$ of participants were fatigue (23 participants), myalgia (9 participants), and headache (9 participants).

Neither deaths nor adverse events leading to study discontinuation occurred.

During the study period, serious adverse events occurred in 2 participants in the Capvaxive group (cholelithiasis and urinary tract infection in 1 participant each), but a causal relationship to the study vaccine was ruled out for both of them.

7.3.4 Global phase III study (CTD 5.3.5.1.9, Study 008, study period, February 2023 to March 2024)

A randomized, double-blind,⁴⁾ parallel-group study was conducted at a total of 44 study sites in 8 countries²⁷⁾ to investigate the safety, tolerability, and immunogenicity of Capvaxive in pneumococcal vaccine-naïve high-risk adults²⁸⁾ aged 18 to 64 years (target sample size, 500 participants [375 in the Capvaxive/saline group, 125 in the PCV15/PPSV23 group]²⁹⁾).

Capvaxive⁹⁾ or PCV15 0.5 mL was administered intramuscularly as the first dose. During a period of Days 60 to 74 postvaccination, saline or PPSV23 0.5 mL was administered intramuscularly as the second dose subsequent to Capvaxive or PCV15, respectively.

Of the 518 randomized participants³⁰⁾ (387 in the Capvaxive/saline group and 131 in the PCV15/PPSV23 group), 516 participants (386 in the Capvaxive/saline group and 130 in the PCV15/PPSV23 group) received the study vaccine at least once, excluding 2 participants (1 in the Capvaxive/saline group and 1 in the PCV15/PPSV23 group). All participants who received the study vaccine at least once were included in the safety analysis set. Among randomized participants, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoint was “serotype-specific OPA GMTs at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23),” and the results are as shown in Table 27.

²⁷⁾ US, Canada, South Korea, Australia, New Zealand, Poland, Chile, and Japan

²⁸⁾ Adults with at least 1 of the following risk factors: diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, or chronic lung disease

²⁹⁾ In this study, immunogenicity and safety were planned to be evaluated using descriptive statistics, and thus no statistical tests of hypotheses were planned. Accordingly, the target sample size was not established based on statistical hypotheses.

³⁰⁾ Randomization was performed using the age category (18-49 years or 50-64 years) and type and number of risk factors for pneumococcal disease (diabetes mellitus only, chronic heart disease only, chronic kidney disease only, chronic liver disease only, chronic lung disease only, or ≥ 2 risk factors) as stratification factors. The study was planned to include adults aged 18 to 49 years constituting $\geq 20\%$ of the overall population and those with risk factors constituting $\geq 5\%$ for each risk factor.

Table 27. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive/saline (N = 386)		PCV15/PPSV23 (N = 130)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
13 shared serotypes				
3	352	216.2 [188.6, 247.8]	104	192.9 [156.7, 237.4]
6A	347	3734.9 [3204.3, 4353.4]	92	2443.8 [1779.0, 3357.1]
7F	355	4261.2 [3781.6, 4801.6]	109	3218.5 [2627.3, 3942.6]
8	357	3460.8 [3083.1, 3884.7]	106	3406.4 [2635.8, 4402.2]
9N	354	7553.9 [6664.1, 8562.5]	107	4548.4 [3696.8, 5596.2]
10A	355	4502.0 [3933.7, 5152.4]	107	2542.0 [1897.0, 3406.2]
11A	358	3761.7 [3375.8, 4191.7]	106	1697.2 [1338.4, 2152.2]
12F	356	2432.3 [2082.7, 2840.6]	107	1364.5 [956.1, 1947.4]
17F	354	10425.3 [9099.2, 11944.7]	104	4331.7 [3248.3, 5776.3]
19A	356	2837.2 [2535.2, 3175.2]	106	2437.2 [2008.5, 2957.5]
20A	357	8091.5 [7169.4, 9132.3]	99	3749.8 [2932.4, 4795.2]
22F	357	4432.7 [3914.2, 5020.0]	108	2717.4 [2201.7, 3353.8]
33F	347	24512.8 [21149.8, 28410.7]	101	11395.1 [8884.5, 14615.3]
8 non-shared serotypes				
15A	353	7274.6 [6398.7, 8270.4]	104	1791.8 [1361.7, 2357.8]
15C	353	7923.1 [6726.7, 9332.3]	107	2269.8 [1651.8, 3118.9]
16F	356	9546.6 [8396.2, 10854.6]	105	1626.2 [1224.4, 2159.8]
23A	346	5875.3 [5005.5, 6896.2]	100	1493.9 [1009.1, 2211.5]
23B	354	2316.9 [1925.9, 2787.3]	108	117.0 [73.4, 186.4]
24F	354	5677.1 [5098.2, 6321.8]	92	1666.8 [1257.6, 2209.1]
31	359	5803.9 [4991.8, 6748.1]	105	360.7 [233.0, 558.5]
35B	347	13141.3 [11584.8, 14906.9]	104	1812.1 [1408.6, 2331.2]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

Table 28 shows incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events and pyrexia within 5 days after the study vaccination were handled as adverse reactions.

Table 28. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	First dose		Second dose	
	Capvaxive/saline (N = 386)	PCV15/PPSV23 (N = 130)	Capvaxive/saline (N = 374)	PCV15/PPSV23 (N = 128)
Local	50.5 (195)	63.8 (83)	9.6 (36)	77.3 (99)
Injection site pain	49.5 (191)	63.1 (82)	8.3 (31)	72.7 (93)
Injection site erythema	7.0 (27)	3.8 (5)	2.7 (10)	23.4 (30)
Injection site swelling	6.5 (25)	7.7 (10)	2.7 (10)	35.2 (45)
Systemic	32.9 (127)	30.8 (40)	20.6 (77)	43.0 (55)
Fatigue	24.6 (95)	24.6 (32)	14.4 (54)	32.8 (42)
Headache	15.8 (61)	12.3 (16)	10.4 (39)	18.0 (23)
Myalgia	8.0 (31)	5.4 (7)	4.5 (17)	11.7 (15)
Pyrexia ^{a)}	1.8 (7)	0	1.9 (7)	4.7 (6)

Incidence % (n), MedDRA version 26.1

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Adverse events occurred in 62.7% (242 of 386) of participants in the Capvaxive/saline group and 75.4% (98 of 130) of participants in the PCV15/PPSV23 group within 30 days after the first dose. The corresponding proportions within 30 days after the second dose were 32.1% (120 of 374) and 82.8% (106 of 128), respectively. Adverse events reported by $\geq 5\%$ of participants in either group were injection site pain (191 participants in the Capvaxive/saline group and 82 participants in the PCV15/PPSV23 group after the first dose, and 31 and 93 participants, respectively, after the second dose), fatigue (95 and 32 participants, respectively, after the first dose, and 55 and 42 participants, respectively, after the

second dose), headache (67 and 17 participants, respectively, after the first dose, and 45 and 24 participants, respectively, after the second dose), myalgia (31 and 7 participants, respectively, after the first dose, and 17 and 15 participants, respectively, after the second dose), injection site erythema (31 and 6 participants, respectively, after the first dose, and 10 and 30 participants, respectively, after the second dose), and injection site swelling (27 and 10 participants, respectively, after the first dose, and 10 and 45 participants, respectively, after the second dose).

Adverse reactions occurred in 58.5% (226 of 386) of participants in the Capvaxive/saline group and 70.8% (92 of 130) of participants in the PCV15/PPSV23 group within 30 days after the first dose. The corresponding proportions within 30 days after the second dose were 22.2% (83 of 374) and 80.5% (103 of 128), respectively. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions, and systemic adverse reactions reported by $\geq 5\%$ of participants in either group were fatigue (92 participants in the Capvaxive/saline group and 29 participants in the PCV15/PPSV23 group after the first dose, and 45 and 38 participants, respectively, after the second dose), headache (60 and 15 participants, respectively, after the first dose, and 36 and 19 participants, respectively, after the second dose), and myalgia (31 and 7 participants, respectively, after the first dose, and 17 and 15 participants, respectively, after the second dose).

Neither deaths nor adverse events leading to study discontinuation occurred.

Serious adverse events occurred in 1.8% (7 of 386) of participants in the Capvaxive/saline group (gastroesophageal reflux disease, obstructive pancreatitis, urosepsis, limb injury, hypoglycaemia, malignant melanoma, asthma, lung disorder, and pulmonary oedema in 1 participant each; some participants had multiple events) and 3.1% (4 of 130) of participants in the PCV15/PPSV23 group (coronary artery stenosis, ventricular tachycardia, syncope, acute kidney injury, and deep vein thrombosis in 1 participant each; some participants had multiple events) during the period from the first dose to the second dose and 0.8% (3 of 374) of participants in the Capvaxive/saline group (pyelonephritis acute, sleep apnoea syndrome, and aortic stenosis in 1 participant each) and 2.3% (3 of 128) of participants in the PCV15/PPSV23 group (pancreatitis acute, pneumonia bacterial, and seizure in 1 participant each) during the period from the second dose to the end of the study. A causal relationship to the study vaccine was ruled out for any of them.

7.3.5 Foreign phase III study (CTD 5.3.5.1.10, Study 007, study period, July 2022 to July 2023)³¹⁾

A randomized, double-blind,⁴⁾ parallel-group study was conducted at a total of 20 study sites in 6 countries³²⁾ to investigate the safety, tolerability, and immunogenicity of Capvaxive in adults infected with human immunodeficiency virus (HIV)³³⁾ aged ≥ 18 years³⁴⁾ regardless of prior pneumococcal

³¹⁾ This study consists of Part A (to compare Capvaxive/saline with PCV15/PPSV23) and Part B (PCV15 administered to participants in the Capvaxive/saline group in Part A). Because Part B is currently ongoing, results from Part A were submitted for the present application.

³²⁾ US, Chile, Belgium, France, South Africa, and Thailand

³³⁾ At the time of screening, antiretroviral therapy had been continued for ≥ 6 weeks; the CD4-positive T-cell count was ≥ 50 cells/ μ L; and the plasma HIV RNA level was $< 50,000$ copies/mL. Adults with medically stable underlying diseases were also included.

³⁴⁾ In participants with prior pneumococcal vaccination, the period from the last pneumococcal vaccination to study vaccination was required to be ≥ 8 weeks for prior vaccination with PCV13 alone, ≥ 4 years for prior vaccination with PCV13/PPSV23, or ≥ 4 years for prior vaccination with PPSV23 alone.

vaccination history (target sample size, 300 participants³⁵⁾ [150 in the Capvaxive/saline group, 150 in the PCV15/PPSV23 group]).

Capvaxive⁹⁾ or PCV15 0.5 mL was administered intramuscularly as the first dose. During a period of Days 56 to 70 postvaccination, saline or PPSV23 0.5 mL was administered intramuscularly as the second dose subsequent to Capvaxive or PCV15, respectively.

Of the 313 randomized participants³⁶⁾ (156 in the Capvaxive/saline group and 157 in the PCV15/PPSV23 group), 312 participants (156 in the Capvaxive/saline group and 156 in the PCV15/PPSV23 group) received the study vaccine at least once, excluding 1 participant in the PCV15/PPSV23 group. Of those who received the study vaccine at least once, 2 participants (1 in the Capvaxive/saline group and 1 in the PCV15/PPSV23 group)³⁷⁾ who received the wrong study vaccine were excluded, and the remaining 310 participants were included in the safety analysis set. Among randomized participants, those without protocol deviations that could have a significant impact on immunogenicity evaluation were defined as the PP population, which was used as the primary immunogenicity analysis set.

The primary immunogenicity endpoint was “serotype-specific OPA GMTs at Day 30 after the study vaccination (30 days after the dose of Capvaxive and 30 days after the dose of PPSV23),” and the results are as shown in Table 29.

³⁵⁾ In this study, immunogenicity and safety were planned to be evaluated using descriptive statistics, and thus no statistical tests of hypotheses were planned. Accordingly, the target sample size was not established based on statistical hypotheses.

³⁶⁾ Randomization was performed using pneumococcal vaccination status (without prior vaccination with PCV13 or PPSV23, with prior vaccination of PCV13 only, with prior vaccination of PPSV23 only, or with prior vaccination of PCV13 and PPSV23) and the CD4-positive T-cell count (≥ 50 cells/ μ L and < 500 cells/ μ L or ≥ 500 cells/ μ L) as stratification factors.

³⁷⁾ Instead of Capvaxive, PCV15 was mistakenly administered to 1 participant in the Capvaxive/saline group, and instead of PPSV23, PCV15 was mistakenly administered to 1 participant in the PCV15/PPSV23 group.

Table 29. Serotype-specific OPA GMTs at Day 30 after the study vaccination (PP population)

Serotype	Capvaxive/saline (N = 156)		PCV15/PPSV23 (N = 156)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
13 shared serotypes				
3	128	170.7 [132.5, 220.0]	126	172.0 [138.4, 213.7]
6A	131	3896.0 [2929.7, 5181.1]	123	3979.5 [3210.6, 4932.5]
7F	135	3482.3 [2815.8, 4306.6]	126	3275.6 [2658.1, 4036.6]
8	137	1847.5 [1470.9, 2320.6]	129	2262.9 [1776.5, 2882.5]
9N	129	5763.0 [4552.8, 7294.7]	126	5970.0 [4786.9, 7445.6]
10A	137	3693.0 [2870.2, 4751.5]	128	3652.8 [2731.4, 4885.1]
11A	134	3742.5 [3050.7, 4591.1]	123	1722.3 [1277.1, 2322.7]
12F	136	2585.4 [1993.5, 3353.0]	128	2292.4 [1653.2, 3178.8]
17F	135	8698.6 [7046.1, 10738.5]	124	5886.3 [4489.8, 7717.1]
19A	137	2178.9 [1777.1, 2671.7]	130	2667.0 [2193.2, 3243.1]
20A	135	7249.1 [5854.9, 8975.4]	130	5753.3 [4634.0, 7143.0]
22F	129	3622.4 [2902.8, 4520.4]	129	3979.8 [3214.5, 4927.1]
33F	123	14642.5 [11314.9, 18948.6]	123	11864.5 [9283.8, 15162.5]
8 non-shared serotypes				
15A	127	5859.0 [4684.9, 7327.4]	124	1970.5 [1555.1, 2496.8]
15C	131	5613.0 [4136.7, 7616.3]	126	2438.0 [1791.5, 3317.7]
16F	129	6703.0 [5494.0, 8178.1]	127	1839.0 [1474.3, 2293.9]
23A	130	5053.5 [3781.3, 6753.5]	111	1674.9 [1209.9, 2318.7]
23B	135	1593.8 [1182.7, 2147.9]	125	151.0 [98.1, 232.6]
24F	132	3725.6 [3161.1, 4391.0]	98	567.9 [375.4, 859.1]
31	137	5699.4 [4435.1, 7324.2]	125	530.8 [364.2, 773.7]
35B	135	11306.2 [9364.7, 13650.1]	128	2977.7 [2425.5, 3655.8]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

Table 30 shows the incidences of local and systemic solicited adverse events within 5 days after the study vaccination. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions.

Table 30. Local and systemic solicited adverse events within 5 days after the study vaccination (safety analysis set)

	First dose		Second dose	
	Capvaxive/saline (N = 155)	PCV15/PPSV23 (N = 155)	Capvaxive/saline (N = 153)	PCV15/PPSV23 (N = 151)
Local	48.4 (75)	61.3 (95)	12.4 (19)	70.9 (107)
Injection site pain	48.4 (75)	60.0 (93)	11.8 (18)	70.2 (106)
Injection site swelling	5.8 (9)	8.4 (13)	2.6 (4)	15.2 (23)
Injection site erythema	2.6 (4)	2.6 (4)	2.6 (4)	9.9 (15)
Systemic	31.6 (49)	29.0 (45)	22.9 (35)	29.8 (45)
Fatigue	21.3 (33)	20.6 (32)	15.0 (23)	23.2 (35)
Headache	16.8 (26)	13.5 (21)	9.8 (15)	8.6 (13)
Myalgia	9.7 (15)	7.7 (12)	3.9 (6)	10.6 (16)
Pyrexia ^{a)}	1.3 (2)	1.9 (3)	0.7 (1)	1.3 (2)

Incidence % (n), MedDRA version 26.0

a) Oral temperature $\geq 38.0^{\circ}\text{C}$

Adverse events occurred in 63.2% (98 of 155) of participants in the Capvaxive/saline group and 70.3% (109 of 155) of participants in the PCV15/PPSV23 group within 30 days after the first dose. The corresponding proportions within 30 days after the second dose were 42.5% (65 of 153) and 76.2% (115 of 151), respectively. Adverse events reported by $\geq 5\%$ of participants in either group were injection site pain (75 participants in the Capvaxive/saline group and 93 participants in the PCV15/PPSV23 group after the first dose, and 18 and 106 participants, respectively, after the second dose), fatigue (33 and 33 participants, respectively, after the first dose, and 23 and 35 participants, respectively, after the second

dose), headache (29 and 21 participants, respectively, after the first dose, and 17 and 14 participants, respectively, after the second dose), myalgia (15 and 12 participants, respectively, after the first dose, and 7 and 16 participants, respectively, after the second dose), injection site swelling (9 and 13 participants, respectively, after the first dose, and 4 and 23 participants, respectively, after the second dose), injection site erythema (4 and 4 participants, respectively, after the first dose, and 4 and 15 participants, respectively, after the second dose), and diarrhoea (2 and 8 participants, respectively, after the first dose, and 0 and 1 participant, respectively, after the second dose).

Adverse reactions occurred in 56.1% (87 of 155) of participants in the Capvaxive/saline group and 67.1% (104 of 155) of participants in the PCV15/PPSV23 group within 30 days after the first dose. The corresponding proportions within 30 days after the second dose were 28.1% (43 of 153) and 72.8% (110 of 151), respectively. All of the local adverse events and pyrexia within 5 days after the study vaccination were assessed as adverse reactions, and systemic adverse reactions reported by $\geq 5\%$ of participants in either group were fatigue (32 participants in the Capvaxive/saline group and 32 participants in the PCV15/PPSV23 group after the first dose, and 21 and 34 participants, respectively, after the second dose), headache (27 and 20 participants, respectively, after the first dose, and 15 and 13 participants, respectively, after the second dose), and myalgia (15 and 12 participants, respectively, after the first dose, and 6 and 16 participants, respectively, after the second dose).

An adverse event leading to death occurred in 1 participant in the Capvaxive/saline group (death of unknown cause³⁸⁾), but a causal relationship to the study vaccine was ruled out for the event.

Serious adverse events occurred in 0.6% (1 of 155) of participants in the Capvaxive/saline group (cerebrovascular accident in 1 participant) and 1.3% (2 of 155) of participants in the PCV15/PPSV23 group (arthritis bacterial and pneumonia in 1 participant each) during the period from the first dose to the second dose and in 2.6% (4 of 153) of participants in the Capvaxive/saline group (chest discomfort, ankle fracture, aphasia, and death in 1 participant each) and 2.6% (4 of 151) of participants in the PCV15/PPSV23 group (neurosyphilis, diffuse large B-cell lymphoma, metastases to meninges, and seizure in 1 participant each) during the period from the second dose to the end of the study. A causal relationship to the study vaccine was ruled out for any of them.

No adverse events leading to study discontinuation occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA evaluated the efficacy of Capvaxive based on results mainly from the following 5 phase III studies, a part of the submitted clinical study data: Cohort 1 (adults aged ≥ 50 years) of a foreign phase

³⁸⁾ 41-year-old man. On Day 62 after the first dose of the study vaccine (Capvaxive), he was diagnosed with mild chronic obstructive pulmonary disease and tracheal stenosis, and on the following day (Day 63 after the first dose of the study vaccine), the second dose of the study vaccine (saline) was administered. On Day 61 after the second dose of the study vaccine (saline), he drank heavily. On Day 62 after the second dose of the study vaccine, he felt unwell and experienced left chest pain. On the following day, he visited a physician and was prescribed an analgesic. On Day 64 after the second dose of the study vaccine, he experienced left chest pain and shallow breathing and then collapsed at home. He was transported to a hospital, but was in cardiopulmonary arrest on arrival and was pronounced dead. At the time of death, chronic obstructive pulmonary disease and tracheal stenosis showed no improvement, but the cause of death remained unknown. A causal relationship to the study vaccine was ruled out.

III study in pneumococcal vaccine-naïve adults aged ≥ 18 years (Study 003), a Japanese phase III study in pneumococcal vaccine-naïve Japanese adults aged ≥ 65 years (Study 009), a global phase III study in adults aged ≥ 50 years with prior pneumococcal vaccination (Study 006), a global phase III study in pneumococcal vaccine-naïve high-risk adults aged 18 to 64 years (Study 008), and a foreign phase III study in adults with HIV infection aged ≥ 18 years (Study 007). Based on the review described in Sections 7.R.1.1 and 7.R.1.2, PMDA concluded that Capvaxive can be expected to have efficacy in adults aged ≥ 65 years and high-risk adults aged ≥ 18 years. Although the clinical study results demonstrated that Capvaxive induced a stronger immune response in healthy adults aged 50 to 64 years than in adults aged ≥ 65 years, it remains unclear whether vaccination with Capvaxive would provide efficacy comparable to that in adults aged ≥ 65 years and high-risk adults. This is because an immunogenicity threshold correlated with protection against pneumococcal disease has not been established, and existing pneumococcal vaccines (PPSV23, PCV20, and PCV15) used as control vaccines have not been approved for the indication for use in healthy adults aged < 65 years in Japan.

7.R.1.1 Efficacy in adults aged ≥ 50 years

The applicant's explanation about the strategy for evaluating the efficacy of Capvaxive and its efficacy in adults aged ≥ 50 years:

For the following reasons, the clinical studies of Capvaxive were designed to explain the efficacy of Capvaxive in this population by comparing its immunogenicity with that of PPSV23, PCV20, or PCV15 approved for the indication of prevention of pneumococcal disease in adults in and outside Japan:

- Since multiple pneumococcal vaccines are approved in and outside Japan, a placebo-controlled study is not feasible.
- An active comparator-controlled study would require an extremely large sample size to evaluate clinical events such as onset of pneumococcal disease and death and thus is not feasible.
- OPA response in adults reflects the biological mechanisms involved in protection against pneumococcal disease. Although an OPA antibody titer correlated with protection against pneumococcal disease has not been established, OPA is considered to play a key role in vaccine-mediated protection against pneumococcal disease, and OPA GMT is considered an important indicator for evaluating the immunogenicity of pneumococcal vaccines (*J Infect Chemother.* 2013;19:412-25).

As described below, (a) efficacy in pneumococcal vaccine-naïve adults aged ≥ 50 years was evaluated based on results from the Cohort 1 of the foreign phase III study (Study 003) and the Japanese phase III study (Study 009), whereas (b) efficacy in adults aged ≥ 50 years with prior pneumococcal vaccination was evaluated based on results from the global phase III study (Study 006). Based on the evaluation results, the applicant considers that Capvaxive can be expected to have efficacy in adults aged ≥ 50 years regardless of prior pneumococcal vaccination history.

(a) Efficacy in pneumococcal vaccine-naïve adults aged ≥ 50 years

Results from Cohort 1 of the foreign phase III study (Study 003) and Japanese phase III study (Study 009) are as follows.

Cohort 1 of foreign phase III study (Study 003)

In Study 003 Cohort 1 (adults aged ≥ 50 years), the applicant planned to evaluate immunogenicity for the 10 serotypes shared by Capvaxive and PCV20 and for the 11 non-shared serotypes unique to Capvaxive as presented below. To achieve the primary immunogenicity objective in Study 003 Cohort 1, satisfying all of the non-inferiority and superiority criteria for primary endpoints, presented below, was required.

- For the 10 shared serotypes, the applicant planned to evaluate non-inferiority of Capvaxive to PCV20 using serotype-specific OPA GMTs at Day 30 after the study vaccination as the primary endpoint. Although WHO recommends comparing the immunogenicity of a new pneumococcal vaccine with that of approved pneumococcal vaccines during vaccine development, it does not clearly define non-inferiority or superiority criteria (*Vaccine*. 2009;27:3681-8). The applicant then specified the non-inferiority margin as 0.5 for OPA GMR and planned to judge that non-inferiority was demonstrated when the lower bound of the 95% CI of OPA GMR of Capvaxive to PCV20 exceeded 0.5 in view of the following reports: In many controlled studies of new vaccines, the non-inferiority margin of 0.5 was specified for GMR (*Vaccine*. 2015;33:1426–32); and in a foreign phase III study in adults comparing PCV13 with PPSV23, the non-inferiority margin of 0.5 was specified for OPA GMRs against the serotypes shared by PCV13 and PPSV23 (*Vaccine*. 2013;31:3577-84).
- For the 11 non-shared serotypes, the applicant planned to evaluate superiority of Capvaxive to PCV20 using (i) serotype-specific OPA GMTs at Day 30 after the study vaccination and (ii) serotype-specific OPA responder rates at Day 30 after the study vaccination as the primary endpoints. The applicant planned to judge that the superiority criterion was met when the lower bound of the 95% CI for the OPA GMR exceeded 2.0 ([i]); and the lower bound of the 95% CI for the difference in OPA responder rates exceeded 10% ([ii]).

Results for the primary endpoints in Study 003 Cohort 1 met the non-inferiority criterion for all 10 shared serotypes and the superiority criteria for 10 of the 11 non-shared serotypes, except for 15C [see Section 7.3.2]. For serotype 15B, for which cross-reactive immunity is expected to be induced by the antigen corresponding to serotype 15C (deOAc15B), the serotype-specific OPA responder rate at Day 30 after the study vaccination was evaluated as the secondary endpoint. The responder rate was 64.7% (95% CI; 61.4%, 67.8%) in the Capvaxive group, and the lower bound of the 95% CI exceeded the acceptable threshold for immune response (50%) specified by the applicant.

Serotype-specific IgG geometric mean concentration (GMC) at Day 30 after the study vaccination was evaluated as the secondary endpoint. For all serotypes, GMCs increased from baseline to Day 30 postvaccination of Capvaxive, and comparison of this parameter between the Capvaxive group and PCV20 group showed a similar trend to that found in comparison of serotype-specific OPA GMTs. For serotype 15C, one of the 11 non-shared serotypes, the serotype-specific OPA GMR at Day 30 after the study vaccination did not meet the superiority criteria, but the OPA GMT against serotype 15C showed a remarkable increase at Day 30 postvaccination of Capvaxive. The OPA geometric mean fold rise (GMFR) from baseline to Day 30 postvaccination of Capvaxive (38.0) was within the range of OPA GMFRs for the other serotypes in the Capvaxive group (10 shared serotypes, 8.4 for serotype 3 to 77.4 for serotype 12F; 11 non-shared serotypes, 7.2 for serotype 35B to 51.4 for serotype 23B). OPA responder rate for serotype 15C was 83.4%, which was within the range of OPA responder rates for the

other serotypes in the Capvaxive group (10 shared serotypes, 64.4% for serotype 19A to 89.0% for serotype 12F; 11 non-shared serotypes, 60.0% for serotype 35B to 85.5% for serotype 23B). IgG antibody response to serotype 15C after the dose of Capvaxive provided similar findings to those on OPA response. Serotype 15B antigen contained in PCV20, which is shown to induce cross-reactive immune response to serotype 15C, is considered partially responsible for the failure to meet the superiority criteria to PCV20 for serotype 15C. The above results on immunogenicity endpoints consistently show that Capvaxive induces immune response to serotype 15C. The applicant considers that Capvaxive can be expected to have efficacy against serotype 15C.

Table 31 shows serotype-specific OPA GMTs at Day 30 after the study vaccination by age category, and serotype-specific OPA GMTs tended to be higher in adults aged 50 to 64 years than in those aged ≥ 65 years. Results on serotype-specific OPA GMTs in each subgroup were generally similar to those in the overall population.

Table 31. Serotype-specific OPA GMTs at Day 30 after the study vaccination by age category (Study 003 Cohort 1, PP population)

Serotype	50-64 years				≥65 years			
	Capvaxive (N = 589)		PCV20 (N = 587)		Capvaxive (N = 590)		PCV20 (N = 590)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
10 shared serotypes								
3	572	284.3 [257.2, 314.2]	577	173.0 [156.5, 191.2]	582	264.1 [237.5, 293.7]	584	180.5 [162.1, 200.9]
6A	569	2598.3 [2299.0, 2936.5]	573	3193.6 [2826.7, 3608.2]	579	2040.3 [1790.6, 2324.9]	580	2783.5 [2438.1, 3177.8]
7F	571	4297.9 [3866.3, 4777.6]	577	3889.0 [3498.9, 4322.7]	581	3085.9 [2748.6, 3464.5]	581	3027.6 [2696.1, 3399.9]
8	571	3007.6 [2733.0, 3309.8]	577	2111.5 [1920.3, 2321.8]	584	2094.2 [1887.5, 2323.4]	581	1556.4 [1399.0, 1731.6]
10A	575	4379.3 [3940.2, 4867.2]	577	5285.7 [4744.2, 5889.1]	586	3464.0 [3106.6, 3862.6]	582	4149.3 [3711.3, 4639.1]
11A	564	3781.9 [3404.4, 4201.3]	571	2518.5 [2270.2, 2793.8]	581	2771.4 [2482.2, 3094.5]	579	1742.5 [1558.4, 1948.4]
12F	574	3559.3 [3165.2, 4002.4]	577	3052.4 [2713.6, 3433.6]	586	1967.5 [1698.4, 2279.2]	584	2058.2 [1772.0, 2390.7]
19A	574	2384.7 [2165.6, 2626.1]	577	3273.8 [2970.5, 3608.0]	585	1916.2 [1728.2, 2124.8]	585	2432.7 [2189.8, 2702.5]
22F	568	4669.0 [4151.9, 5250.5]	579	5485.0 [4876.4, 6169.6]	579	3219.3 [2854.6, 3630.7]	575	4153.1 [3674.9, 4693.6]
33F	570	17551.7 [15421.3, 19976.5]	575	13974.8 [12275.3, 15909.6]	584	10518.0 [9186.7, 12042.2]	582	9899.3 [8644.1, 11336.8]
11 non-shared serotypes								
9N	570	8523.5 [7671.7, 9469.9]	571	1777.4 [1605.7, 1967.5]	577	6562.5 [5894.9, 7305.6]	579	1516.2 [1364.4, 1684.8]
15A	550	5879.2 [5217.0, 6625.4]	552	1815.6 [1609.7, 2047.8]	557	4666.0 [4085.8, 5328.7]	550	1391.5 [1213.6, 1595.5]
15C	570	5697.5 [4964.8, 6538.3]	574	2508.8 [2186.1, 2879.0]	583	3141.2 [2708.4, 3643.2]	584	1720.6 [1482.7, 1996.7]
16F	571	5698.6 [5085.1, 6386.0]	576	989.4 [885.4, 1105.5]	580	4175.8 [3721.5, 4685.5]	577	725.2 [646.9, 812.9]
17F	568	9798.1 [8548.2, 11230.7]	576	517.9 [454.7, 589.8]	580	6190.2 [5407.5, 7086.3]	580	410.2 [359.5, 467.9]
20A	575	7713.5 [6860.3, 8672.8]	574	679.6 [605.3, 763.1]	586	4829.4 [4288.8, 5438.0]	581	589.3 [523.2, 663.8]
23A	561	4808.7 [4086.0, 5659.2]	547	568.2 [481.2, 671.0]	571	2918.0 [2455.5, 3467.6]	557	376.8 [314.4, 451.6]
23B	575	1408.8 [1179.3, 1683.0]	577	107.1 [89.8, 127.8]	585	835.8 [699.5, 998.5]	583	108.0 [90.2, 129.3]
24F	570	2981.1 [2577.4, 3447.9]	563	81.1 [69.9, 94.0]	583	2508.2 [2168.8, 2900.7]	567	61.4 [52.7, 71.4]
31	570	4029.7 [3434.6, 4727.9]	575	192.3 [164.8, 224.5]	583	2420.7 [2069.0, 2832.4]	579	109.5 [93.6, 128.1]
35B	573	9208.9 [8313.5, 10200.7]	578	1575.8 [1428.2, 1738.7]	580	7898.0 [7096.0, 8790.5]	581	1213.8 [1091.7, 1349.5]

a) GMT was calculated using a cLDA model. This model used natural log-transformed antibody titers at baseline and at Day 30 postvaccination as response variables and included timepoint, vaccine group, and the interaction between timepoint and vaccine group. An unstructured covariance matrix was used to model correlations among repeated measurements.

Japanese phase III study (Study 009)

In Study 009, the applicant planned to employ PPSV23 as control vaccine, which was approved for use in individuals aged ≥65 years in Japan and is used for routine immunization, and to evaluate immunogenicity for 12 shared serotypes, cross-reactive serotype 15B, and 9 non-shared serotypes separately as presented below. To achieve the primary immunogenicity objective in Study 009, satisfying all of the non-inferiority and superiority criteria for primary endpoints, presented below, was required.

- For the 12 shared serotypes and the cross-reactive serotype 15B, the applicant planned to evaluate non-inferiority of Capvaxive to PPSV23 using serotype-specific OPA GMTs at Day 30 after the study vaccination as the primary endpoint. As in Study 003, the non-inferiority margin of 0.5 was specified,

and the applicant planned to judge that non-inferiority was demonstrated when the lower bound of the 95% CI of OPA GMR of Capvaxive to PPSV23 exceeded 0.5.

- For the non-shared serotype 15C, PPSV23 contains serotype 15B, which is structurally similar to serotype 15C (*Clin Vaccine Immunol.* 2017;24:e00099-17), and in Studies 001 and 002, cross-reactive immune response to non-shared serotype 15C was induced in the PPSV23 group [see Section 7.2]. However, PPSV23 has not been demonstrated to prevent onset of infection with serotype 15C pathogens, and the applicant planned to evaluate superiority of Capvaxive to PPSV23 using serotype-specific OPA GMTs at Day 30 after the study vaccination as the primary endpoint. The superiority margin of 1.0 was specified for GMR as is commonly done. For the 8 non-shared serotypes other than serotype 15C, which are not included in PPSV23, superiority to PPSV23 was evaluated using OPA responder rates, rather than serotype-specific OPA GMTs, as the primary endpoint. The superiority margin of 0% was specified for the difference in OPA responder rate, because 0% is commonly used in clinical studies and was also adopted in a clinical study of PCV13 in adults for comparison with PPSV23 (*Vaccine.* 2013;31:3577-84). Then, the applicant planned to judge that the superiority of Capvaxive to PPSV23 was demonstrated when the lower bound of the 95% CI for the OPA GMR exceeded 1.0 for non-shared serotype 15C; and the lower bound of the 95% CI for the difference in OPA responder rates exceeded 0% for the 8 non-shared serotypes, except for serotype 15C.

Results on the primary endpoints in Study 009 met the non-inferiority criterion for all 12 shared serotypes and the cross-reactive serotype 15B and the superiority criteria for both non-shared serotype 15C and 8 non-shared serotypes, achieving the primary immunogenicity objective [see Section 7.3.1].

Results on the secondary endpoints showed that serotype-specific OPA GMTs at Day 30 after the study vaccination for the 8 non-shared serotypes (except for serotype 15C) were higher in the Capvaxive group than in the PPSV23 group (Table 32). Serotype-specific OPA responder rates were similar between the Capvaxive group and PPSV23 group for the 12 shared serotypes and higher in the Capvaxive group than in the PPSV23 group for the cross-reactive serotype 15B and non-shared serotype 15C (Table 33). For the 21 serotypes and the immunologically cross-reactive serotype 15B, serotype-specific OPA GMFRs from baseline to Day 30 after the study vaccination were similar between the treatment groups for the 12 shared serotypes and higher in the Capvaxive group than in the PPSV23 group for the 9 non-shared serotypes (Table 34). Serotype-specific IgG GMCs increased from baseline to Day 30 postvaccination of Capvaxive for all serotypes included in Capvaxive, and comparison of this parameter between the Capvaxive group and PPSV23 group showed a similar trend to that found in comparison of serotype-specific OPA GMT.

Table 32. Serotype-specific OPA GMTs at Day 30 after the study vaccination (Study 009, PP population)

Serotype	Capvaxine (N = 225)		PPSV23 (N = 225)		GMR [two-sided 95% CI] ^{a)}
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	
8 non-shared serotypes					
6A	223	1341.5 [1095.7, 1642.4]	224	591.5 [482.0, 726.0]	2.27 [1.73, 2.97]
15A	224	2763.7 [2324.9, 3285.3]	219	800.2 [669.3, 956.8]	3.45 [2.71, 4.41]
16F	225	4032.6 [3491.7, 4657.3]	225	1186.9 [1026.0, 1373.0]	3.40 [2.82, 4.09]
23A	218	2078.7 [1669.5, 2588.3]	194	687.8 [535.9, 882.7]	3.02 [2.18, 4.19]
23B	223	1390.1 [1082.3, 1785.3]	223	198.6 [153.8, 256.4]	7.00 [5.05, 9.71]
24F	225	2526.3 [2203.2, 2896.9]	218	1026.6 [887.3, 1187.7]	2.46 [2.02, 3.00]
31	225	2251.6 [1837.2, 2759.4]	225	235.9 [192.0, 289.9]	9.54 [7.35, 12.39]
35B	225	4847.2 [4213.4, 5576.4]	225	1029.0 [894.0, 1184.4]	4.71 [3.94, 5.63]

a) GMT, GMR, and 95% CI were calculated using a cLDA model. This model used natural log-transformed antibody titers at baseline and at Day 30 postvaccination as response variables and included timepoint, vaccine group, the interaction between timepoint and vaccine group, age category (65-74 years and ≥ 75 years), and the interaction between timepoint and age category. An unstructured covariance matrix was used to model correlations among repeated measurements.

Table 33. Serotype-specific OPA responder rate at Day 30 after the study vaccination (Study 009, PP population)

Serotype	Capvaxine (N = 225)	PPSV23 (N = 225)	Difference between groups [two-sided 95% CI] ^{a)}
12 shared serotypes			
3	73.8 (138/187)	71.3 (139/195)	2.5 [-6.5, 11.4]
7F	68.5 (148/216)	69.6 (151/217)	-1.1 [-9.8, 7.6]
8	79.8 (170/213)	81.0 (171/211)	-1.1 [-8.6, 6.4]
9N	57.6 (102/177)	58.8 (104/177)	-1.2 [-11.5, 9.0]
10A	69.3 (140/202)	59.7 (114/191)	9.6 [0.2, 19.0]
11A	69.3 (140/202)	55.8 (110/197)	13.5 [4.0, 22.8]
12F	84.3 (182/216)	74.3 (153/206)	10.0 [2.3, 17.7]
17F	66.1 (123/186)	62.6 (119/190)	3.4 [-6.3, 13.0]
19A	58.1 (126/217)	61.0 (130/213)	-3.1 [-12.3, 6.1]
20A	54.1 (111/205)	42.3 (83/196)	11.8 [2.0, 21.3]
22F	62.0 (129/208)	52.3 (104/199)	9.8 [0.2, 19.3]
33F	58.0 (123/212)	63.7 (137/215)	-5.8 [-15.0, 3.4]
Non-shared serotype			
15C	81.0 (162/200)	65.4 (125/191)	15.5 [6.8, 24.1]
Cross-reactive serotype			
15B	67.2 (125/186)	54.6 (101/185)	12.7 [2.7, 22.4]

Proportion of participants % (number of applicable participants/number of participants analyzed)

a) The difference between groups and the two-sided 95% CI were calculated using the stratified Miettinen-Nurminen method with age category (65-74 years and ≥ 75 years) as a stratification factor.

Table 34. Serotype-specific OPA GMFRs at Day 30 after the study vaccination (Study 009, PP population)

Serotype	Capvaxive (N = 225)		PPSV23 (N = 225)	
	No. of participants analyzed	GMFR [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMFR [two-sided 95% CI] ^{a)}
12 shared serotypes				
3	187	7.2 [6.1, 8.5]	195	7.2 [6.1, 8.5]
7F	216	10.0 [8.0, 12.6]	217	9.8 [8.0, 12.1]
8	213	20.6 [16.4, 25.8]	211	19.1 [15.5, 23.7]
9N	177	6.9 [5.6, 8.5]	177	6.6 [5.3, 8.1]
10A	202	10.1 [8.2, 12.4]	191	7.6 [5.9, 9.9]
11A	202	13.6 [10.5, 17.7]	197	7.3 [5.7, 9.4]
12F	216	32.2 [25.7, 40.3]	206	17.1 [13.2, 22.1]
17F	186	9.8 [7.8, 12.4]	190	7.1 [5.9, 8.6]
19A	217	6.7 [5.5, 8.1]	213	5.8 [4.8, 6.9]
20A	205	5.6 [4.7, 6.6]	196	4.1 [3.4, 4.8]
22F	208	8.9 [6.9, 11.5]	199	6.9 [5.4, 8.8]
33F	212	6.4 [5.2, 7.8]	215	7.3 [6.0, 8.8]
9 non-shared serotypes				
6A	184	9.4 [7.5, 11.6]	190	3.7 [3.0, 4.5]
15A	181	6.7 [5.3, 8.5]	169	2.0 [1.6, 2.4]
15C	200	19.1 [15.2, 24.1]	191	9.3 [7.4, 11.7]
16F	197	4.7 [4.0, 5.6]	201	1.5 [1.4, 1.7]
23A	144	5.9 [4.2, 8.2]	111	1.8 [1.4, 2.4]
23B	201	26.2 [20.5, 33.6]	199	4.2 [3.3, 5.4]
24F	198	3.8 [3.1, 4.6]	175	1.5 [1.2, 1.8]
31	219	13.6 [10.6, 17.3]	214	1.4 [1.2, 1.6]
35B	221	5.5 [4.6, 6.5]	218	1.2 [1.0, 1.3]
Cross-reactive serotype				
15B	186	7.4 [5.7, 9.5]	185	4.8 [3.7, 6.2]

a) GMFR was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

As described above, in Study 003 Cohort 1 in non-Japanese adults aged ≥ 50 years, the non-inferiority or superiority criteria for the primary endpoints were met for all serotypes except for serotype 15C, and in Study 009 in Japanese adults aged ≥ 65 years, the non-inferiority or superiority criteria for the primary endpoints were met for all serotypes. In Study 003 Cohort 1, the superiority criteria for the primary endpoints were not met for serotype 15C, but in both Studies 003 and 009, the OPA GMT against serotype 15C showed a remarkable increase at Day 30 postvaccination in the Capvaxive group, and the induced immune response was not greatly different from that found for the other serotypes. In view of the above findings, the applicant considers that Capvaxive can be expected to have efficacy against serotype 15C.

Results in Japanese aged ≥ 65 years in Study 009 and results from the subgroup analysis by age category in Study 003 Cohort 1 indicated that Capvaxive induced similar immune responses in both Japanese and non-Japanese adults aged ≥ 65 years. Furthermore, results by age category in Study 003 Cohort 1 showed that the immune response tended to decrease with aging; the immune response was higher in adults aged 50 to 64 years than in those aged ≥ 65 years. In Japanese adults aged 50 to 64 years, the immune response is therefore also expected to be induced at least to an extent observed in Japanese adults aged ≥ 65 years.

(b) Efficacy in adults aged ≥ 50 years with prior pneumococcal vaccination

In the global phase III study in adults aged ≥ 50 years with prior pneumococcal vaccination²²⁾ (Study 006), serotype-specific OPA GMTs at Day 30 after the study vaccination, the primary endpoint, showed increases for all 21 serotypes included in Capvaxive (Tables 21, 23, and 25). In Cohort 1 (with prior

PPSV23 vaccination), the GMTs were similar between the Capvaxive group and PCV15 group for the 6 shared serotypes and higher in the Capvaxive group than in the PCV15 group for the 15 non-shared serotypes. In Cohort 2 (with prior PCV13 vaccination), the GMTs were similar between the Capvaxive group and PPSV23 group for the 12 shared serotypes and higher in the Capvaxive group than in the PPSV23 group for the 9 non-shared serotypes.

In all cohorts, serotype-specific IgG GMCs increased from baseline to Day 30 postvaccination of Capvaxive for all 21 serotypes included in Capvaxive, and in Cohorts 1 and 2, comparison of this parameter between the Capvaxive group and PCV15 or PPSV23 group showed a similar trend to that found in comparison of serotype-specific OPA GMTs.

Based on serotype-specific OPA GMTs at Day 30 after the study vaccination by age category in each cohort in Study 006, serotype-specific OPA GMTs in adults aged 50 to 64 years are considered unlikely to be greatly below those in adults aged ≥ 65 years, although comparisons between age categories have limitations because of the small number of participants aged 50 to 64 years.

Tables 35 and 36 show serotype-specific OPA GMTs at Day 30 after the study vaccination, the primary endpoint, in the Japanese population in Cohorts 1 and 2 in Study 006, showing similar results to those in the overall population. Participants in the Japanese population were all ≥ 65 years, and none of the Japanese adults were enrolled in Cohort 3.

Table 35. Serotype-specific OPA GMTs at Day 30 after the study vaccination in the Japanese population (Study 006 Cohort 1, PP population)

Serotype	Capvaxive (N = 31)		PCV15 (N = 19)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
6 shared serotypes				
3	30	219.6 [134.8, 357.9]	19	209.9 [124.2, 354.8]
6A	29	967.1 [551.2, 1696.5]	17	1042.5 [494.0, 2199.6]
7F	31	1723.5 [1174.2, 2529.8]	19	960.8 [553.5, 1668.0]
19A	30	974.7 [647.8, 1466.5]	18	1301.6 [844.6, 2005.9]
22F	30	1349.3 [936.7, 1943.6]	18	717.8 [342.9, 1502.7]
33F	27	3609.9 [2236.0, 5827.9]	17	2323.4 [1432.1, 3769.6]
15 non-shared serotypes				
8	30	615.6 [414.6, 914.2]	19	234.9 [112.9, 488.8]
9N	31	2820.3 [2148.7, 3701.8]	18	2898.5 [1789.7, 4694.3]
10A	30	1018.9 [549.9, 1888.2]	18	450.8 [215.3, 944.1]
11A	28	1107.8 [575.6, 2132.0]	18	130.4 [42.8, 397.7]
12F	31	294.7 [140.3, 618.9]	19	85.5 [31.9, 229.4]
15A	25	2697.1 [1933.5, 3762.1]	16	541.7 [200.4, 1464.4]
15C	31	1029.6 [529.7, 2001.1]	19	672.1 [249.5, 1810.6]
16F	31	1784.6 [1264.2, 2519.1]	19	322.7 [199.4, 522.4]
17F	31	2343.7 [1697.5, 3236.1]	19	1888.0 [1144.0, 3116.0]
20A	31	1771.3 [1171.9, 2677.4]	18	1004.1 [511.4, 1971.5]
23A	30	535.4 [242.8, 1180.4]	15	160.3 [50.6, 507.5]
23B	31	349.8 [169.7, 721.1]	19	126.4 [47.9, 333.5]
24F	29	1182.6 [588.4, 2377.0]	18	79.3 [31.5, 199.5]
31	28	1362.9 [755.2, 2459.5]	18	62.6 [23.1, 169.8]
35B	28	3284.7 [2254.5, 4785.8]	18	441.1 [147.1, 1323.1]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

Table 36. Serotype-specific OPA GMTs at Day 30 after the study vaccination in the Japanese population (Study 006 Cohort 2, PP population)

Serotype	Capvaxive (N = 11)		PPSV23 (N = 2)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT ^{b)}
12 shared serotypes				
3	11	287.3 [101.4, 813.9]	2	964.6
7F	9	1972.5 [1377.2, 2825.2]	2	3580.9
8	11	1639.2 [923.9, 2908.5]	2	1783.2
9N	10	7505.3 [3489.9, 16140.8]	1	4261.0
10A	10	3824.5 [2078.1, 7038.6]	2	95.5
11A	11	2447.1 [1448.1, 4135.2]	2	1459.8
12F	11	1562.2 [563.9, 4327.9]	2	2241.9
17F	11	7077.4 [5021.8, 9974.4]	2	1068.5
19A	10	1863.0 [1222.4, 2839.2]	2	2775.7
20A	11	5800.0 [2830.0, 11886.6]	2	576.5
22F	10	2010.2 [480.0, 8419.0]	2	143.6
33F	8	4893.9 [2648.9, 9041.8]	2	6516.3
9 non-shared serotypes				
6A	10	2065.4 [1043.1, 4089.6]	1	85.0
15A	9	5185.0 [3311.2, 8119.1]	0	-
15C	11	4585.2 [2278.5, 9227.1]	2	127.2
16F	11	3358.1 [1700.8, 6630.3]	2	875.1
23A	11	2853.8 [1479.2, 5505.6]	2	103.8
23B	11	885.6 [248.8, 3152.2]	2	477.5
24F	11	4247.8 [2402.7, 7510.0]	1	10.5
31	11	2721.2 [1355.5, 5462.9]	2	74.5
35B	11	5050.0 [2349.4, 10854.9]	2	124.7

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

b) Because of the small number of participants, the 95% CI was not calculated.

The above results showed that immune response induced in adults aged ≥ 50 years by Capvaxive was similar to that induced by the existing pneumococcal vaccine (PCV20, PPSV23, or PCV15) for serotypes shared with the existing vaccine and stronger than that induced by the existing pneumococcal vaccine for non-shared serotypes, irrespective of prior pneumococcal vaccination.

PMDA's view:

The applicant proposed that the efficacy of Capvaxive in adults aged ≥ 65 years and high-risk adults be assessed by comparing its immunogenicity with that of PCV20 and PPSV23, which are indicated for the prevention of pneumococcal disease in adults aged ≥ 65 years and high-risk adults. Although an immunogenicity threshold correlated with protection against pneumococcal disease has not been established, PMDA considers this approach to be reasonable to some extent, given that clinical studies evaluating clinical events are not feasible and that OPA has been reported to play a key role in vaccine efficacy against pneumococcal disease. Based on development experience of PCV13, the applicant evaluated the non-inferiority of Capvaxive to the control vaccine for shared serotypes and the cross-reactive serotype 15B (only in Study 009), and the superiority of Capvaxive to the control vaccine for non-shared serotypes in Study 003 Cohort 1 and Study 009. The above applicant's evaluation strategy is acceptable. The control vaccine was PCV20 in Study 003 and PPSV23 in Study 009, and their use is also acceptable in view of approvals and recommendations of pneumococcal vaccines in and outside Japan as well as routine immunization status in Japan.

In Study 009 in pneumococcal vaccine-naïve Japanese adults aged ≥ 65 years, the non-inferiority or superiority of Capvaxive to PPSV23 was demonstrated based on results on the primary endpoints. PMDA thus considers that efficacy of Capvaxive can be expected. In Study 009, serotype-specific OPA GMTs against the cross-reactive serotype 15B, which is not included among the antigens contained in Capvaxive, was evaluated as one of the primary endpoints, and Capvaxive was shown to induce an immune response against this serotype. However, in Study 003 Cohort 1 in pneumococcal vaccine-naïve non-Japanese adults aged ≥ 50 years, the OPA GMT against serotype 15C at Day 30 after the study vaccination, one of the primary endpoints, did not meet the superiority criterion for Capvaxive versus PCV20. The applicant explained that the efficacy of Capvaxive can be expected for serotype 15C because OPA GMT remarkably increased from baseline to Day 30 postvaccination of Capvaxive, and the OPA GMFR from baseline to Day 30 postvaccination of Capvaxive and OPA responder rate at Day 30 were within the range for the other serotypes in the Capvaxive group in Study 003. The applicant's explanation is understandable. In addition, because in Study 009, results on the primary endpoints for serotype 15C met the superiority criteria for Capvaxive to PPSV23, and in Japanese and foreign studies, antibody titers against serotype 15C changed with time in a similar manner, the above applicant's explanation about expected efficacy of Capvaxive for serotype 15C is acceptable. Results from the subgroup analysis by age category in Study 003 Cohort 1 showed that the serotype-specific OPA GMTs in the subgroup aged ≥ 65 years was generally similar to those in the overall population. Results on immunogenicity in adults aged ≥ 65 years in Study 003 Cohort 1 and those in Study 009 were not substantially different. Furthermore, Study 006 indicated that Capvaxive would induce immune response regardless of prior pneumococcal vaccination history. Based on the above, Capvaxive can be expected to have efficacy in Japanese adults aged ≥ 65 years regardless of prior pneumococcal vaccination history.

For use in adults aged 50 to 64 years, the subgroup analysis by age category in Study 003 Cohort 1 demonstrated that immune response induced in the subgroup aged 50 to 64 years was stronger than that in the subgroup aged ≥ 65 years. However, whether efficacy of Capvaxive in healthy adults aged 50 to 64 years is similar to that in adults aged ≥ 65 years and high-risk adults remains unclear because existing pneumococcal vaccines (PCV20, PPSV23, and PCV15) used as control vaccines have not been approved for the indication in healthy adults aged < 65 years in Japan.

Efficacy in high-risk adults aged 50 to 64 years is reviewed together with efficacy in high-risk adults aged 18 to 49 years in Section 7.R.1.2.

7.R.1.2 Efficacy in high-risk adults

The applicant's explanation about efficacy in high-risk adults:

Although various risk factors may lead to pneumococcal diseases, individuals who have diseases or symptoms potentially associated with decreased systemic immune function, decreased immune protection from infections by organ impairment with chronic underlying diseases, and decreased host defense by anatomical causes can be recognized as individuals at high risk, according to reports in and outside Japan ("Guidance for pneumococcal vaccination in high-risk individuals aged 6 to 64 years (in Japanese)" Version 3, April 2025 by the Joint Committee of the Vaccine Working Group, Scientific Assembly of Infections and Tuberculosis, the Japanese Respiratory Society/the Committee of Vaccines,

the Japanese Association for Infectious Diseases/the Japanese Society for Vaccinology, *Open Forum Infect Dis.* 2015;2:ofv020, etc.). More specifically, individuals with the following diseases or conditions are included: Chronic heart disease, lung disease, liver disease or kidney disease, diabetes mellitus, immunocompromised condition by underlying disease or treatment or such condition suspected, congenital or acquired asplenia, sickle cell disease or other haemoglobinopathy, and decreased host defense by anatomical causes such as cochlear implant and chronic cerebrospinal fluid leak. The above individuals are listed as ones at high risk of pneumococcal diseases in package inserts of PCV15 and PCV20. Efficacy of Capvaxine in high-risk adults was evaluated based on results from Cohort 1 of the foreign phase III study (Study 003), global phase III study (Study 008), and foreign phase III study (Study 007), as presented below. Capvaxine can be expected to have efficacy in high-risk adults irrespective of number or type of risk factors.

Cohort 1 of foreign phase III study (Study 003)

In Study 003 Cohort 1 (adults aged ≥ 50 years), approximately 36% of participants had one or more prespecified risk factors for pneumococcal disease (alcoholism, chronic heart disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes mellitus, or smoking). Proportions of participants by the number of risk factors (0, 1, or ≥ 2) and by risk factor were generally similar between the vaccine groups (Table 37).

Table 37. Proportions of participants by risk factor (Study 003 Cohort 1, overall population)

	Capvaxine (N = 1,179)	PCV20 (N = 1,177)
Without risk factors	62.1 (732)	65.3 (768)
With risk factors	37.9 (447)	34.7 (409)
Diabetes mellitus	18.0 (212)	15.5 (182)
Smoking	11.8 (139)	11.3 (133)
Chronic lung disease	11.5 (135)	11.1 (131)
Chronic kidney disease	2.2 (26)	1.9 (22)
Chronic heart disease	2.1 (25)	1.4 (16)
Chronic liver disease	1.8 (21)	1.9 (22)
Alcoholism	0.3 (3)	0.3 (3)

Proportion of participants % (number of participants)

A subgroup analysis by number of risk factors revealed that serotype-specific OPA GMTs and serotype-specific OPA responder rates at Day 30 after the study vaccination in individual subgroups (number of risk factors, 0, 1, ≥ 2) were consistent and generally similar to those in the overall population, although the numbers of participants were unbalanced among the subgroups (Tables 38 and 39).

Table 38. Serotype-specific OPA GMTs at Day 30 after the study vaccination by number of risk factors (Study 003 Cohort 1, PP population)

Sero-type	Without risk factors				With 1 risk factor				With ≥2 risk factors			
	Capvaxine (N = 732)		PCV20 (N = 768)		Capvaxine (N = 347)		PCV20 (N = 328)		Capvaxine (N = 100)		PCV20 (N = 81)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
10 shared serotypes												
3	717	286.6 [262.0, 313.6]	759	173.7 [159.0, 189.7]	340	265.1 [230.9, 304.3]	321	195.9 [169.6, 226.3]	97	221.3 [166.2, 294.6]	81	138.9 [101.6, 189.7]
6A	711	2409.4 [2157.2, 2691.1]	752	3019.5 [2706.3, 3369.0]	340	2277.9 [1924.8, 2695.7]	321	3088.1 [2599.8, 3668.0]	97	1579.0 [1109.4, 2247.2]	80	2303.6 [1575.7, 3367.8]
7F	714	3900.7 [3532.6, 4307.1]	757	3607.7 [3272.1, 3977.7]	341	3312.5 [2875.0, 3816.5]	321	3130.5 [2712.5, 3612.8]	97	3066.5 [2278.8, 4126.5]	80	2902.5 [2099.4, 4012.6]
8	717	2699.3 [2477.0, 2941.6]	756	1881.2 [1728.3, 2047.6]	342	2318.8 [2032.9, 2644.9]	321	1730.6 [1508.8, 1985.1]	96	1872.5 [1367.8, 2563.4]	81	1484.8 [1056.8, 2086.3]
10A	721	4148.7 [3773.9, 4560.7]	758	4661.3 [4238.0, 5126.9]	343	3586.6 [3128.6, 4111.6]	321	4701.1 [4072.0, 5427.4]	97	3188.8 [2332.0, 4360.3]	80	4559.3 [3252.6, 6390.8]
11A	708	3394.6 [3088.8, 3730.6]	751	2139.0 [1951.3, 2344.7]	341	2892.9 [2487.1, 3364.9]	320	2024.1 [1730.2, 2367.8]	96	3266.4 [2531.8, 4214.1]	79	1923.9 [1456.3, 2541.6]
12F	720	2694.7 [2392.3, 3035.4]	758	2592.5 [2303.9, 2917.2]	343	2721.5 [2314.2, 3200.4]	323	2416.0 [2043.8, 2855.9]	97	2139.1 [1429.8, 3200.2]	80	1935.5 [1243.9, 3011.7]
19A	719	2212.0 [2023.9, 2417.6]	759	2882.1 [2638.7, 3148.0]	343	2038.9 [1779.8, 2335.7]	322	2764.0 [2399.2, 3184.3]	97	1945.6 [1544.2, 2451.5]	81	2440.4 [1896.8, 3139.7]
22F	711	4070.6 [3666.5, 4519.2]	756	4882.0 [4401.0, 5415.7]	339	3414.4 [2908.3, 4008.6]	318	4697.1 [3980.3, 5543.0]	97	4187.4 [3079.6, 5693.7]	80	4082.9 [2928.0, 5693.1]
33F	716	14595.1 [12996.2, 16390.7]	757	12770.4 [11386.6, 14322.5]	342	11848.7 [9894.0, 14189.7]	321	11131.3 [9266.0, 13372.1]	96	12276.4 [8820.2, 17087.1]	79	6761.7 [4761.5, 9602.2]
11 non-shared serotypes												
9N	709	7845.2 [7160.5, 8595.4]	750	1727.4 [1583.2, 1884.8]	341	7027.2 [6048.3, 8164.6]	320	1436.9 [1237.2, 1668.9]	97	6449.4 [4890.2, 8505.6]	80	1664.7 [1245.4, 2225.3]
15A	696	5257.0 [4708.8, 5869.0]	716	1717.3 [1537.0, 1918.6]	319	5112.7 [4295.8, 6085.0]	308	1345.1 [1123.9, 1609.9]	92	5289.8 [3813.4, 7337.9]	78	1535.2 [1082.7, 2176.8]
15C	714	4610.0 [4075.0, 5215.1]	755	2239.0 [1981.6, 2529.7]	342	3656.0 [2988.8, 4472.0]	322	1793.4 [1462.2, 2199.7]	97	3485.2 [2422.0, 5015.1]	81	1750.7 [1190.1, 2575.5]
16F	714	5009.3 [4531.8, 5537.1]	753	924.3 [839.7, 1017.5]	340	5021.4 [4298.5, 5865.8]	319	714.1 [609.6, 836.4]	97	3544.5 [2645.8, 4748.4]	81	698.3 [511.5, 953.3]
17F	711	7674.0 [6789.6, 8673.6]	755	454.2 [404.7, 509.8]	340	8141.7 [6833.0, 9701.0]	321	493.6 [414.4, 588.0]	97	6831.3 [4855.7, 9610.7]	80	420.3 [296.2, 596.3]
20A	720	6443.7 [5800.4, 7158.5]	755	640.9 [578.2, 710.5]	344	5724.7 [4894.0, 6696.5]	319	637.0 [543.4, 746.9]	97	5124.5 [3836.7, 6844.7]	81	513.5 [378.8, 696.0]
23A	704	3757.4 [3239.5, 4358.1]	717	485.8 [417.4, 565.5]	332	3942.9 [3158.3, 4922.5]	310	399.2 [315.1, 505.9]	96	3002.2 [1914.0, 4709.1]	77	491.4 [310.8, 776.9]
23B	719	1174.3 [1001.1, 1377.4]	756	104.1 [89.0, 121.9]	344	983.7 [784.2, 1234.0]	323	116.8 [92.5, 147.4]	97	808.1 [498.8, 1309.0]	81	100.6 [60.3, 167.9]
24F	716	2669.7 [2353.8, 3027.9]	739	74.8 [65.8, 85.0]	340	2975.9 [2443.9, 3623.8]	313	64.6 [52.6, 79.2]	97	2448.5 [1618.2, 3704.8]	78	57.7 [37.1, 89.8]
31	716	3260.2 [2834.7, 3749.7]	754	156.5 [136.7, 179.2]	340	3001.8 [2421.4, 3721.3]	319	118.8 [95.9, 147.1]	97	2800.4 [1896.0, 4136.2]	81	140.0 [92.2, 212.6]
35B	718	8507.4 [7778.7, 9304.2]	758	1434.6 [1316.6, 1563.2]	339	9137.1 [7849.9, 10635.3]	321	1315.9 [1131.0, 1531.1]	96	6775.8 [5242.7, 8757.0]	80	1217.5 [929.3, 1595.2]

a) GMT, GMR, and 95% CI were calculated using a cLDA model. This model used natural log-transformed antibody titers at baseline and at Day 30 postvaccination as response variables and included timepoint, vaccine group, the interaction between timepoint and vaccine group, age category (50-64 years, 65-74 years, ≥75 years), and the interaction between timepoint and age category. An unstructured covariance matrix was used to model correlations among repeated measurements.

Table 39. Serotype-specific OPA responder rate at Day 30 after the study vaccination by number of risk factors (Study 003 Cohort 1, PP population)

Serotype	Without risk factors		With 1 risk factor		With ≥ 2 risk factors	
	Capvaxive (N = 732)	PCV20 (N = 768)	Capvaxive (N = 347)	PCV20 (N = 328)	Capvaxive (N = 100)	PCV20 (N = 81)
11 non-shared serotypes						
9N	65.2 (376/577)	20.3 (130/641)	63.7 (167/262)	18.4 (49/266)	64.2 (52/81)	22.5 (16/71)
15A	66.8 (300/449)	37.6 (173/460)	67.2 (133/198)	32.3 (62/192)	63.0 (29/46)	33.3 (18/54)
15C	85.3 (515/604)	75.5 (459/608)	79.6 (215/270)	71.3 (186/261)	82.1 (64/78)	73.5 (50/68)
16F	69.6 (401/576)	21.3 (136/638)	77.6 (201/259)	16.5 (42/254)	69.3 (52/75)	31.9 (22/69)
17F	74.6 (402/539)	9.2 (58/629)	78.2 (197/252)	10.1 (26/258)	76.1 (54/71)	9.2 (6/65)
20A	68.8 (438/637)	10.1 (67/666)	66.5 (189/284)	8.4 (23/275)	58.5 (48/82)	10.0 (7/70)
23A	78.8 (383/486)	37.3 (180/483)	77.8 (168/216)	33.3 (63/189)	83.9 (47/56)	43.5 (27/62)
23B	86.4 (554/641)	48.9 (328/671)	84.0 (246/293)	51.1 (141/276)	83.9 (73/87)	50.0 (37/74)
24F	79.4 (470/592)	6.5 (37/569)	82.9 (213/257)	5.8 (14/240)	81.6 (62/76)	6.3 (4/63)
31	76.7 (442/576)	19.2 (121/629)	77.8 (200/257)	14.3 (37/258)	70.9 (56/79)	19.4 (13/67)
35B	60.4 (351/581)	6.9 (45/656)	60.8 (160/263)	6.1 (16/263)	53.4 (39/73)	8.7 (6/69)

Proportion of participants % (number of applicable participants/number of participants analyzed)

Global phase III study (Study 008)

Study 008 included pneumococcal vaccine-naïve adults aged 18 to 64 years³⁹⁾ at risk of pneumococcal disease (with diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, or chronic lung disease). More specifically in terms of risk factors for pneumococcal disease, this study was comprised of 194 participants with diabetes mellitus only (37.6%), 84 participants with chronic heart disease only (16.3%), 23 participants with chronic kidney disease only (4.5%), 34 participants with chronic liver disease only (6.6%), 99 participants with chronic lung disease only (19.2%), and 82 participants with ≥ 2 risk factors (15.9%).

The primary endpoint was serotype-specific OPA GMTs at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23). The serotype-specific OPA GMTs in the Capvaxive/saline group were similar to those in the PCV15/PPSV23 group for 13 shared serotypes and higher than those in the PCV15/PPSV23 group for 8 non-shared serotypes [see Section 7.3.4]. Results on serotype-specific OPA responder rates at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23) were similar to those on serotype-specific OPA GMTs. Results on serotype-specific IgG GMC and IgG responder rates at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23) were also similar to those on the above OPA response parameters.

A subgroup analysis by number of risk factors revealed that serotype-specific OPA GMTs at Day 30 after the study vaccination in individual subgroups (number of risk factors, 1 or ≥ 2) were consistent and generally similar to those in the overall population, although the numbers of participants were unbalanced among the subgroups (Table 40).

The serotype-specific OPA GMTs at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23) in the Japanese population were generally similar to that in the overall population (Table 41).

³⁹⁾ Median age (range) was 55 (18-64 years).

Table 40. Serotype-specific OPA GMTs at Day 30 after the study vaccination by number of risk factors (Study 008, PP population)

Sero-type	With 1 risk factor				With ≥2 risk factors			
	Capvaxive/saline (N = 326)		PCV15/PPSV23 (N = 108)		Capvaxive/saline (N = 60)		PCV15/PPSV23 (N = 22)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
13 shared serotypes								
3	299	220.2 [190.2, 254.9]	88	181.0 [143.8, 227.9]	53	195.1 [133.2, 285.7]	16	273.3 [168.0, 444.7]
6A	297	3974.4 [3402.4, 4642.5]	78	2388.1 [1706.9, 3341.2]	50	2582.1 [1514.3, 4402.7]	14	2778.7 [974.5, 7923.4]
7F	303	4127.0 [3616.0, 4710.2]	93	3295.4 [2641.7, 4110.8]	52	5134.6 [3917.8, 6729.4]	16	2805.7 [1591.0, 4947.9]
8	304	3532.0 [3118.7, 4000.1]	90	3716.6 [2826.8, 4886.4]	53	3078.9 [2238.5, 4234.7]	16	2086.3 [985.3, 4417.7]
9N	303	7725.1 [6788.7, 8790.7]	91	4714.4 [3717.6, 5978.4]	51	6612.3 [4341.8, 10070.2]	16	3709.6 [2636.4, 5219.7]
10A	303	4437.9 [3807.9, 5172.2]	91	2660.6 [1918.7, 3689.5]	52	4894.1 [3858.1, 6208.4]	16	1961.1 [998.5, 3851.8]
11A	305	3919.8 [3496.4, 4394.5]	91	1666.6 [1272.1, 2183.4]	53	2968.2 [2152.3, 4093.5]	15	1895.3 [1243.6, 2888.5]
12F	305	2544.2 [2160.8, 2995.6]	92	1494.6 [1034.0, 2160.2]	51	1858.9 [1153.9, 2994.8]	15	780.8 [223.1, 2732.9]
17F	303	10537.3 [9099.7, 12202.0]	88	4202.5 [3052.2, 5786.4]	51	9784.1 [6717.6, 14250.4]	16	5116.1 [2507.9, 10436.6]
19A	304	2915.3 [2594.2, 3276.1]	90	2519.7 [2044.8, 3105.0]	52	2420.8 [1677.7, 3493.0]	16	2021.2 [1150.0, 3552.4]
20A	306	8013.9 [7063.9, 9091.7]	83	3902.0 [2950.7, 5160.1]	51	8573.3 [5793.8, 12686.2]	16	3050.5 [1828.5, 5089.2]
22F	304	4456.8 [3887.9, 5108.9]	92	2757.8 [2176.5, 3494.5]	53	4297.4 [3158.3, 5847.4]	16	2496.0 [1576.7, 3951.5]
33F	297	26116.1 [22218.5, 30697.5]	86	11632.1 [8808.4, 15360.9]	50	16824.9 [11848.0, 23892.3]	15	10126.8 [5631.2, 18211.5]
8 non-shared serotypes								
15A	302	7352.0 [6395.9, 8451.1]	89	1904.9 [1405.8, 2581.3]	51	6832.6 [4865.0, 9596.0]	15	1246.0 [644.9, 2407.5]
15C	302	7477.3 [6286.6, 8893.6]	92	2271.2 [1580.8, 3263.3]	51	11163.9 [6886.6, 18097.9]	15	2260.8 [1333.2, 3834.0]
16F	304	9470.3 [8236.1, 10889.4]	90	1601.5 [1163.8, 2203.9]	52	10005.6 [7141.2, 14018.8]	15	1782.6 [974.8, 3260.1]
23A	294	6070.3 [5117.3, 7200.6]	85	1614.9 [1058.5, 2463.7]	52	4885.2 [3072.7, 7766.6]	15	960.9 [301.4, 3063.6]
23B	301	2249.4 [1844.2, 2743.6]	92	113.4 [68.5, 187.8]	53	2740.8 [1636.4, 4590.5]	16	139.8 [35.9, 545.0]
24F	303	5598.9 [5002.7, 6266.2]	81	1820.2 [1405.6, 2357.1]	51	6164.9 [4380.9, 8675.3]	11	871.5 [183.5, 4138.9]
31	306	5753.1 [4906.6, 6745.6]	89	394.8 [246.6, 632.0]	53	6106.4 [3858.4, 9664.3]	16	218.4 [60.6, 787.0]
35B	297	13393.3 [11682.8, 15354.2]	88	1893.4 [1429.3, 2508.2]	50	11739.2 [8384.4, 16436.4]	16	1423.5 [788.2, 2570.8]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

Table 41. Serotype-specific OPA GMTs at Day 30 after the study vaccination in the Japanese population (Study 008, PP population)

Serotype	Capvaxive/saline (N = 31)		PCV15/PPSV23 (N = 5)	
	No. of participants analyzed	GMT [95% CI] ^{a)}	No. of participants analyzed	GMT [95% CI] ^{a)}
13 shared serotypes				
3	29	191.6 [117.4, 312.9]	5	154.7 [37.7, 634.4]
6A	30	2778.1 [1903.8, 4053.9]	5	3412.0 [2535.7, 4591.3]
7F	30	6160.4 [4331.6, 8761.4]	5	4516.6 [1825.5, 11174.7]
8	30	3525.5 [2390.3, 5199.8]	5	4054.2 [2352.8, 6985.8]
9N	29	5711.4 [4220.8, 7728.5]	5	3978.0 [1022.5, 15475.8]
10A	28	3754.0 [2460.2, 5728.4]	4	715.7 [69.9, 7325.0]
11A	30	2799.3 [1911.7, 4099.0]	5	1369.7 [215.2, 8716.4]
12F	30	1471.8 [926.3, 2338.5]	5	1209.1 [21.7, 67350.5]
17F	30	6811.6 [4321.6, 10736.1]	5	4641.1 [820.3, 26257.7]
19A	30	2021.6 [1230.7, 3320.6]	5	2924.5 [1009.1, 8475.3]
20A	30	6692.3 [4325.3, 10354.5]	5	3969.7 [433.5, 36351.0]
22F	30	3027.4 [2142.0, 4278.9]	5	5855.2 [3492.2, 9817.2]
33F	30	21611.8 [14035.9, 33276.6]	5	10804.9 [2087.0, 55938.5]
8 non-shared serotypes				
15A	29	5595.0 [3494.7, 8957.5]	5	1890.6 [339.0, 10545.2]
15C	28	8722.3 [5188.1, 14664.0]	4	1089.8 [108.1, 10988.9]
16F	29	8572.3 [5529.4, 13289.8]	5	1337.3 [144.2, 12403.5]
23A	30	4695.1 [3095.4, 7121.5]	5	1106.2 [56.6, 21628.8]
23B	28	2213.3 [1117.3, 4384.3]	5	720.5 [22.2, 23418.7]
24F	28	4312.9 [3175.7, 5857.3]	4	722.4 [7.8, 67058.0]
31	30	4331.5 [2773.0, 6766.1]	5	157.0 [5.0, 4911.5]
35B	29	8952.7 [6115.1, 13106.9]	5	2457.2 [191.0, 31604.3]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

Foreign phase III study (Study 007)

Study 007 enrolled adults with HIV infection aged ≥ 18 years,⁴⁰⁾ and the primary endpoint was serotype-specific OPA GMTs at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23). The serotype-specific OPA GMTs in the Capvaxive/saline group were similar to those in the PCV15/PPSV23 group for 13 shared serotypes and higher than those in the PCV15/PPSV23 group for 8 non-shared serotypes [see Section 7.3.5]. Results on serotype-specific OPA responder rates at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23) were similar to those on serotype-specific OPA GMTs. Results on serotype-specific IgG GMC and IgG responder rates at Day 30 after the study vaccination (30 days after the dose of Capvaxive or PPSV23) were also similar to those on the above OPA response parameters.

Table 42 shows results from a subgroup analysis by CD4-positive T-cell count. Serotype-specific OPA GMTs tended to be higher in the subgroup with CD4-positive T-cells ≥ 500 cells/ μ L than in the subgroup with CD4-positive T-cells ≥ 50 cells/ μ L and < 500 cells/ μ L, but as observed in the overall population, the values in the Capvaxive/saline group were similar to those in the PCV15/PPSV23 group for 13 shared serotypes and higher than those in the PCV15/PPSV23 group for 8 non-shared serotypes.

⁴⁰⁾ Median age (range) was 45 (19-86 years).

Table 42. Serotype-specific OPA GMTs at Day 30 after the study vaccination by CD4-positive T-cell count (Study 007, PP population)

Serotype	CD4-positive T-cell count ≥ 50 cells/ μ L and < 500 cells/ μ L				CD4-positive T-cell count ≥ 500 cells/ μ L			
	Capvaxine/saline (N = 38)		PCV15/PPSV23 (N = 41)		Capvaxine/saline (N = 118)		PCV15/PPSV23 (N = 115)	
	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}	No. of participants analyzed	GMT [two-sided 95% CI] ^{a)}
13 shared serotypes								
3	32	168.5 [98.3, 288.6]	34	116.4 [73.6, 184.2]	96	171.5 [128.0, 229.8]	92	198.6 [155.7, 253.4]
6A	31	2326.3 [1274.0, 4247.5]	34	2853.3 [1804.9, 4510.8]	100	4571.4 [3310.4, 6312.8]	89	4518.7 [3553.7, 5745.7]
7F	34	3848.2 [2508.3, 5903.9]	35	2705.0 [1479.1, 4946.7]	101	3367.1 [2625.9, 4317.5]	91	3525.9 [2939.3, 4229.5]
8	34	1436.2 [827.9, 2491.5]	35	2357.6 [1434.2, 3875.4]	103	2007.7 [1568.8, 2569.3]	94	2228.6 [1681.7, 2953.5]
9N	32	4297.1 [2391.3, 7722.0]	35	4778.9 [3018.7, 7565.5]	97	6348.9 [4940.3, 8159.0]	91	6503.5 [5049.1, 8376.9]
10A	34	3334.6 [2128.8, 5223.6]	33	2484.6 [1365.6, 4520.7]	103	3819.5 [2816.9, 5179.0]	95	4176.1 [2989.7, 5833.3]
11A	34	3686.2 [2477.1, 5485.5]	32	1045.3 [557.2, 1960.8]	100	3761.8 [2952.8, 4792.4]	91	2052.9 [1463.9, 2879.0]
12F	33	2012.9 [1245.9, 3252.3]	35	1498.3 [679.5, 3303.9]	103	2801.2 [2055.4, 3817.8]	93	2690.3 [1909.7, 3789.9]
17F	33	7396.2 [4463.5, 12256.0]	35	4576.8 [2379.6, 8803.0]	102	9167.2 [7279.4, 11544.6]	89	6498.6 [4895.5, 8626.6]
19A	34	2148.4 [1414.8, 3262.3]	35	1900.7 [1306.7, 2764.7]	103	2189.1 [1726.2, 2776.1]	95	3021.5 [2405.1, 3795.9]
20A	34	6048.8 [3773.9, 9695.0]	35	5153.1 [3438.6, 7722.4]	101	7704.6 [6053.9, 9805.5]	95	5991.6 [4621.1, 7768.6]
22F	33	3333.7 [2213.4, 5021.0]	35	2976.8 [1678.9, 5278.1]	96	3727.3 [2856.5, 4863.6]	94	4434.1 [3609.9, 5446.5]
33F	30	13304.3 [7684.7, 23033.2]	34	7793.6 [4494.4, 13514.6]	93	15102.2 [11220.2, 20327.3]	89	13930.7 [10680.9, 18169.1]
8 non-shared serotypes								
15A	33	3887.0 [2389.6, 6322.5]	32	2500.2 [1364.8, 4580.1]	94	6766.9 [5279.3, 8673.6]	92	1813.9 [1418.4, 2319.6]
15C	33	2997.9 [1366.4, 6577.5]	33	2367.5 [1321.8, 4240.4]	98	6933.0 [5088.7, 9445.6]	93	2463.5 [1703.5, 3562.6]
16F	32	6858.8 [4646.5, 10124.6]	34	1199.4 [726.5, 1980.2]	97	6652.4 [5258.5, 8415.8]	93	2150.0 [1694.4, 2728.1]
23A	32	3612.3 [1935.1, 6743.2]	26	911.1 [473.0, 1754.9]	98	5639.0 [4054.6, 7842.4]	85	2017.8 [1390.4, 2928.3]
23B	33	939.0 [435.8, 2023.1]	33	82.3 [34.8, 194.7]	102	1891.4 [1389.1, 2575.3]	92	187.8 [113.8, 309.8]
24F	30	3313.6 [2373.0, 4627.1]	28	441.5 [195.1, 999.1]	102	3856.3 [3185.6, 4668.2]	70	628.1 [384.9, 1025.0]
31	34	3596.8 [2195.9, 5891.6]	33	338.9 [148.5, 773.3]	103	6634.7 [4965.9, 8864.2]	92	623.5 [408.5, 951.7]
35B	33	10322.0 [6661.7, 15993.5]	34	2678.6 [1905.6, 3765.0]	102	11644.2 [9442.7, 14359.1]	94	3094.0 [2400.5, 3987.7]

a) GMT was calculated by back-transforming the natural log-transformed mean, and the 95% CI was calculated by back-transforming the confidence interval based on the t-distribution of the natural log-transformed mean.

PMDA considers that the applicant's explanation is acceptable, namely that, based on results from Study 003 Cohort 1, Study 008, and Study 007, Capvaxine can be expected to have efficacy in high-risk adults irrespective of the number or type of risk factors.

7.R.1.3 Persistence of efficacy

The applicant's explanation about the long-term efficacy of Capvaxine:

Persistence of immunogenicity of Capvaxine was not evaluated as part of the clinical studies included in the present application, but currently a randomized, double-blind, active comparator-controlled, phase III study (Study V116-010) is ongoing to evaluate the safety, tolerability, and immunogenicity of Capvaxine in comparison with those of PPSV23 in pneumococcal vaccine-naïve non-Japanese adults

aged ≥ 50 years after a single dose of either vaccine. In this study, a sub-study for long-term immunogenicity evaluation is incorporated with the exploratory objective to monitor immune responses including OPA and IgG responses over a period of 24 months postvaccination and scheduled to end at the ■ quarter of 20■. Furthermore, to evaluate the efficacy of Capvaxive against pneumococcal pneumonia, a real-world observational study using a test-negative case control design is currently being planned.

In general, PCVs are considered to induce a T-cell-dependent immune response and generate memory B cells. Although clinical studies conducted to date have evaluated the durability of immune responses induced by PCVs for only 2 to 5 years (*Clin Infect Dis.* 2017;65:787-95, *Clin Infect Dis.* 2015;61:1835-8, etc.), the Advisory Committee on Immunization Practices (ACIP), in a recent evaluation of PCVs, estimated the duration of efficacy to be 15 years (*Vaccine.* 2025;44:126567).

Because induction of Th1- and Th2-related cytokines was confirmed in non-clinical studies of Capvaxive [see Section 3.1.4], Capvaxive is considered capable of generating memory B cells through induction of a T-cell-dependent immune response. Therefore, Capvaxive is expected to induce immune responses that persist longer than those induced by polysaccharide vaccines and can be expected to provide long-term protective efficacy comparable to that of approved PCVs.

PMDA accepted the applicant's explanation that Capvaxive can be expected to have long-term efficacy comparable to that of other PCVs, although data on the durability of efficacy of Capvaxive are not currently available.

7.R.2 Safety

The applicant's explanation about the safety of Capvaxive:

(a) Safety of Capvaxive in adults aged ≥ 50 years

As described below, safety in pneumococcal vaccine-naïve adults aged ≥ 50 years and safety in adults aged ≥ 50 years with prior pneumococcal vaccination were evaluated based on results from Cohort 1 of the foreign phase III study (Study 003) and Japanese phase III study (Study 009), and the global phase III study (Study 006), respectively. Safety of Capvaxive in adults aged ≥ 50 years regardless of prior pneumococcal vaccination history was similar to that of PCV20, PPSV23, or PCV15, and no safety concerns specific to Japanese individuals were identified. Capvaxive is thus considered to have acceptable safety in this population.

- Safety in pneumococcal vaccine-naïve adults aged ≥ 50 years

Results from Cohort 1 of the foreign phase III study (Study 003) and Japanese phase III study (Study 009) are as follows.

Cohort 1 of foreign phase III study (Study 003)

Table 43 shows a summary of adverse events in Study 003 Cohort 1.

Table 43. Summary of adverse events (Study 003 Cohort 1, safety analysis set)

	Capvaxive (N = 1,177)	PCV20 (N = 1,175)
All adverse events ^{a)}	58.2 (685)	66.2 (778)
Solicited adverse events ^{b)}	51.0 (600)	60.3 (708)
Solicited injection site reactions	41.4 (487)	53.6 (630)
Solicited systemic reactions	28.4 (334)	27.5 (323)
Non-solicited adverse events ^{a)c)}	21.3 (251)	21.4 (252)
All adverse reactions ^{a)}	51.7 (609)	60.9 (715)
Non-solicited adverse reactions ^{a)c)}	6.4 (75)	6.4 (75)
Grade ≥ 3 adverse events ^{a)d)}	2.3 (27)	3.4 (40)
Death ^{e)}	0.3 (4)	0.2 (2)
Serious adverse events ^{e)}	1.6 (19)	2.0 (24)
Serious adverse reactions ^{e)}	0	0
Adverse events leading to discontinuation ^{e)}	0	0

Incidence % (n)

a) Events occurring within 30 days after the study vaccination

b) Events occurring within 5 days after the study vaccination

c) Except for solicited adverse events occurring within 5 days after the study vaccination

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Events occurring during the study period

Of solicited adverse events within 5 days after the study vaccination, solicited injection site reactions, pyrexia, and solicited systemic reactions occurred at generally similar incidences between the vaccine groups, except for injection site pain with a lower incidence in the Capvaxive group than in the PCV20 group. Most of the events were mild (Grade 1) or moderate (Grade 2) and had similar severity between the vaccine groups. Severe (Grade 3) or higher solicited adverse events occurred in 7 participants (0.6%) in the Capvaxive group and in 12 participants (1.0%) in the PCV20 group. Although Grade 4 pyrexia was reported in 1 participant in the Capvaxive group, the reported value was considered to have been entered incorrectly by the participant based on the clinical symptoms observed. Most events resolved within 3 days.

The most common adverse events occurring within 30 days after the study vaccination were the solicited adverse events of injection site pain, fatigue, headache, injection site erythema, injection site swelling, and myalgia, and their incidences were generally similar between the vaccine groups, except for that of injection site pain. Most of the events were mild (Grade 1) or moderate (Grade 2) and had similar severity between the vaccine groups. Grade 3 or higher adverse events occurred in 0.7% (8 participants) of the Capvaxive group and 1.4% (16 participants) of the PCV20 group for Grade 3 events, and in 1.6% (19 participants) and 2.0% (24 participants), respectively, for Grade 4 events. No individual event occurred in more than 0.5% of participants. Systemic adverse reactions reported in $\geq 5\%$ of participants in either group were the solicited adverse events of fatigue, headache, and myalgia. The incidences of non-solicited adverse reactions were low and similar between the vaccine groups.

Deaths and serious adverse events occurring during the study period are as presented in Section 7.3.2, and, a causal relationship to the study vaccine was ruled out for all of them. No adverse events leading to study discontinuation occurred.

Tables 44 and 45 show a safety summary and solicited adverse events by age category. Incidences of adverse events tended to be higher in adults aged 50 to 64 years than in those aged ≥ 65 years, but the incidences showed a similar trend in all age categories.

Table 44. Summary of adverse events by age category (Study 003 Cohort 1, safety analysis set)

	50-64 years		≥65 years	
	Capvaxive (N = 587)	PCV20 (N = 585)	Capvaxive (N = 590)	PCV20 (N = 590)
All adverse events ^{a)}	62.9 (369)	72.8 (426)	53.6 (316)	59.7 (352)
Solicited adverse events ^{b)}	57.2 (336)	69.1 (404)	44.7 (264)	51.5 (304)
Solicited injection site reactions	48.7 (286)	64.3 (376)	34.1 (201)	43.1 (254)
Solicited systemic reactions	32.4 (190)	32.0 (187)	24.4 (144)	23.1 (136)
Non-solicited adverse events ^{a)c)}	21.1 (124)	21.7 (127)	21.5 (127)	21.2 (125)
All adverse reactions ^{a)}	57.9 (340)	68.5 (401)	45.6 (269)	53.2 (314)
Non-solicited adverse reactions ^{a)c)}	7.0 (41)	6.2 (36)	5.8 (34)	6.6 (39)
Grade ≥3 adverse events ^{a)d)}	2.2 (13)	2.2 (13)	2.4 (14)	4.6 (27)
Death ^{e)}	0.3 (2)	0	0.3 (2)	0.3 (2)
Serious adverse events ^{e)}	1.4 (8)	1.4 (8)	1.9 (11)	2.7 (16)
Serious adverse reactions ^{e)}	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days after the study vaccination

b) Events occurring within 5 days after the study vaccination

c) Except for solicited adverse events occurring within 5 days after the study vaccination

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Events occurring during the study period

Table 45. Incidences of solicited adverse events by age category (Study 003 Cohort 1, safety analysis set)

	50-64 years		≥65 years	
	Capvaxive (N = 587)	PCV20 (N = 585)	Capvaxive (N = 590)	PCV20 (N = 590)
Solicited injection site reactions	48.7 (286)	64.3 (376)	34.1 (201)	43.1 (254)
Injection site pain	48.0 (282)	62.2 (364)	30.8 (182)	41.2 (243)
Injection site swelling	6.8 (40)	10.3 (60)	5.3 (31)	6.4 (38)
Injection site erythema	5.6 (33)	6.8 (40)	5.3 (31)	5.8 (34)
Solicited systemic reactions	32.4 (190)	32.0 (187)	24.4 (144)	23.1 (136)
Fatigue	22.7 (133)	22.6 (132)	17.6 (104)	16.6 (98)
Headache	14.3 (84)	15.9 (93)	8.6 (51)	10.0 (59)
Myalgia	7.0 (41)	7.4 (43)	4.9 (29)	6.1 (36)
Pyrexia	1.0 (6)	1.0 (6)	1.5 (9)	1.5 (9)

Incidence % (n)

Japanese phase III study (Study 009)

Table 46 shows a summary of adverse events in Study 009.

Table 46. Summary of adverse events (Study 009, safety analysis set)

	Capvaxive (N = 225)	PPSV23 (N = 225)
All adverse events ^{a)}	38.2 (86)	44.4 (100)
Solicited adverse events ^{b)}	32.0 (72)	44.0 (99)
Solicited injection site reactions	30.2 (68)	39.1 (88)
Solicited systemic reactions	10.7 (24)	14.7 (33)
Non-solicited adverse events ^{a)c)}	10.7 (24)	4.9 (11)
All adverse reactions ^{a)}	35.6 (80)	43.1 (97)
Non-solicited adverse reactions ^{a)c)}	5.3 (12)	2.2 (5)
Grade ≥ 3 adverse events ^{a)d)}	0.4 (1)	0.4 (1)
Death ^{e)}	0	0
Serious adverse events ^{e)}	0.4 (1)	0
Serious adverse reactions ^{e)}	0	0
Adverse events leading to discontinuation ^{e)}	0	0

Incidence % (n)

a) Events occurring within 30 days after the study vaccination

b) Events occurring within 5 days after the study vaccination

c) Except for solicited adverse events occurring within 5 days after the study vaccination

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Events occurring during the study period

Of solicited adverse events within 5 days after the study vaccination, solicited injection site reactions, pyrexia, and solicited systemic reactions occurred at generally similar incidences between the vaccine groups, except for injection site pain with a lower incidence in the Capvaxive group. Most of the events were mild (Grade 1) and had similar severity between the vaccine groups. No severe (Grade 3) or higher solicited adverse events occurred in the Capvaxive group, whereas a Grade 3 solicited adverse event occurred in 1 participant (0.4%) in the PPSV23 group. Most events resolved within 3 days.

The most common adverse events occurring within 30 days after the study vaccination were the solicited adverse events of injection site pain, injection site erythema, fatigue, and injection site swelling, and their incidences were generally similar between the vaccine groups. Most of the events were mild (Grade 1) and had similar severity between the vaccine groups. Of severe (Grade 3) or higher adverse events, a Grade 3 event occurred in 0 participants in the Capvaxive group and in 1 participant (0.4%) in the PPSV23 group, and a Grade 4 event occurred in 1 participant (0.4%) in the Capvaxive group and in 0 participants in the PPSV23 group. Systemic adverse reactions reported in $\geq 5\%$ of participants in either group were limited to the solicited adverse event of fatigue. The incidences of non-solicited adverse reactions were low and similar between the vaccine groups.

During the study period, neither deaths nor adverse events leading to discontinuation occurred. A serious adverse event occurred in 1 participant in the Capvaxive group (lacunar infarction), but a causal relationship to Capvaxive was ruled out for the event.

- Safety in adults aged ≥ 50 years with prior pneumococcal vaccination

Results from the global phase III study (Study 006) were investigated. Table 47 shows a summary of adverse events.

Table 47. Summary of adverse events (Study 006 Cohorts 1, 2, and 3, safety analysis set)

	Cohort 1		Cohort 2		Cohort 3
	Capvaxive (N = 230)	PCV15 (N = 117)	Capvaxive (N = 174)	PPSV23 (N = 85)	Capvaxive (N = 105)
All adverse events ^{a)}	51.3 (118)	64.1 (75)	52.9 (92)	65.9 (56)	52.4 (55)
Solicited adverse events ^{b)}	46.5 (107)	55.6 (65)	49.4 (86)	61.2 (52)	48.6 (51)
Solicited injection site reactions	40.0 (92)	47.9 (56)	43.1 (75)	54.1 (46)	43.8 (46)
Solicited systemic reactions	20.9 (48)	21.4 (25)	25.9 (45)	23.5 (20)	24.8 (26)
Non-solicited adverse events ^{a)c)}	13.9 (32)	17.9 (21)	12.6 (22)	16.5 (14)	10.5 (11)
All adverse reactions ^{a)}	46.5 (107)	56.4 (66)	50.0 (87)	61.2 (52)	48.6 (51)
Non-solicited adverse reactions ^{a)c)}	5.2 (12)	1.7 (2)	2.9 (5)	2.4 (2)	2.9 (3)
Grade ≥ 3 adverse events ^{a)d)}	3.0 (7)	5.1 (6)	4.0 (7)	3.5 (3)	3.8 (4)
Death ^{e)}	0	0	0	0	0
Serious adverse events ^{e)}	0.9 (2)	3.4 (4)	1.1 (2)	3.5 (3)	1.9 (2)
Serious adverse reactions ^{e)}	0.4 (1)	0	0	0	0
Adverse events leading to discontinuation ^{e)}	0	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days after the study vaccination

b) Events occurring within 5 days after the study vaccination

c) Except for solicited adverse events occurring within 5 days after the study vaccination

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Events occurring during the study period

Of solicited adverse events within 5 days after the study vaccination in Cohorts 1 and 2, solicited injection site reactions, pyrexia, and solicited systemic reactions occurred at generally similar incidences between the vaccine groups, except for injection site swelling with a higher incidence in the PPSV23 group than in the Capvaxive group in Cohort 2. Most of the events were mild (Grade 1) or moderate (Grade 2) and had similar severity between the vaccine groups. Severe (Grade 3) solicited adverse events occurred in 4 participants (1.7%) in the Capvaxive group and 2 participants (1.7%) in the PCV15 group in Cohort 1; 5 participants (2.9%) in the Capvaxive group and 0 participants in the PPSV23 group in Cohort 2; and 2 participants (1.9%) in the Capvaxive group in Cohort 3. No Grade 4 solicited adverse events occurred. Most events resolved within 3 days.

Of adverse events occurring within 30 days after the study vaccination, the most commonly reported adverse events (incidence $\geq 5\%$) across 3 cohorts were solicited adverse events of injection site pain, fatigue, injection site swelling (except for the Capvaxive group in Cohort 2), injection site erythema, headache, and myalgia (except for the PCV15 group in Cohort 1). Incidences of each adverse event in Cohorts 1 and 2 were generally similar between the vaccine groups except for injection site swelling in Cohort 2. Most of the events were mild (Grade 1) or moderate (Grade 2) and had similar severity between the vaccine groups. Of severe (Grade 3) or higher adverse events, Grade 3 events occurred in 4 participants (1.7%) in the Capvaxive group and 2 participants (1.7%) in the PCV15 group, and Grade 4 events occurred in 3 participants (1.3%) in the Capvaxive group and 4 participants (3.4%) in the PCV15 group in Cohort 1; Grade 3 events occurred in 5 participants (2.9%) in the Capvaxive group and 0 participants in the PPSV23 group, and Grade 4 events occurred in 2 participants (1.1%) in the Capvaxive group and 3 participants (3.5%) in the PPSV23 group in Cohort 2; and Grade 3 events occurred in 2 participants (1.9%) and Grade 4 events occurred in 2 participants (1.9%) in the Capvaxive group in Cohort 3. Systemic adverse reactions reported in $\geq 5\%$ of participants in any group across the 3 cohorts were the solicited adverse events of fatigue, myalgia (except in the PCV15 group in Cohort 1), and headache. The incidences of non-solicited adverse reactions were low and similar across all groups.

During the study period, neither deaths nor adverse events leading to discontinuation occurred. Of serious adverse events described in Section 7.3.3, injection site cellulitis in the Capvaxive group in Cohort 1, for which a causal relationship to Capvaxive could not be ruled out, resolved.

Tables 48 and 49 show a summary of adverse events and solicited adverse events by age category. Incidences of adverse events tended to be higher in adults aged 50 to 64 years than in those aged ≥ 65 years, but the incidences in the Capvaxive group showed a similar trend to those in the PCV15 group and PPSV23 group in all age categories.

Table 48. Summary of adverse events by age category (Study 006 Cohorts 1, 2, and 3, safety analysis set)

	50-64 years					≥ 65 years				
	Cohort 1		Cohort 2		Cohort 3	Cohort 1		Cohort 2		Cohort 3
	Capvaxive (N = 48)	PCV15 (N = 25)	Capvaxive (N = 80)	PPSV23 (N = 39)	Capvaxive (N = 17)	Capvaxive (N = 182)	PCV15 (N = 92)	Capvaxive (N = 94)	PPSV23 (N = 46)	Capvaxive (N = 88)
All adverse events ^{a)}	58.3 (28)	68.0 (17)	57.5 (46)	74.4 (29)	47.1 (8)	49.5 (90)	63.0 (58)	48.9 (46)	58.7 (27)	53.4 (47)
Solicited adverse events ^{b)}	50.0 (24)	56.0 (14)	56.3 (45)	69.2 (27)	47.1 (8)	45.6 (83)	55.4 (51)	43.6 (41)	54.3 (25)	48.9 (43)
Solicited injection site reactions	47.9 (23)	56.0 (14)	52.5 (42)	64.1 (25)	47.1 (8)	37.9 (69)	45.7 (42)	35.1 (33)	45.7 (21)	43.2 (38)
Solicited systemic reactions	20.8 (10)	28.0 (7)	22.5 (18)	30.8 (12)	23.5 (4)	20.9 (38)	19.6 (18)	28.7 (27)	17.4 (8)	25.0 (22)
Non-solicited adverse events ^{a,c)}	29.2 (14)	16.0 (4)	8.8 (7)	17.9 (7)	11.8 (2)	9.9 (18)	18.5 (17)	16.0 (15)	15.2 (7)	10.2 (9)
All adverse reactions ^{a)}	54.2 (26)	56.0 (14)	57.5 (46)	69.2 (27)	47.1 (8)	44.5 (81)	56.5 (52)	43.6 (41)	54.3 (25)	48.9 (43)
Non-solicited adverse reactions ^{a,c)}	14.6 (7)	4.0 (1)	2.5 (2)	2.6 (1)	0	2.7 (5)	1.1 (1)	3.2 (3)	2.2 (1)	3.4 (3)
Grade ≥ 3 adverse events ^{a,d)}	6.3 (3)	8.0 (2)	1.3 (1)	0	11.8 (2)	2.1 (4)	4.4 (4)	6.4 (6)	6.5 (3)	2.3 (2)
Death ^{e)}	0	0	0	0	0	0	0	0	0	0
Serious adverse events ^{e)}	2.1 (1)	8.0 (2)	1.3 (1)	0	0	0.5 (1)	2.2 (2)	1.1 (1)	6.5 (3)	2.3 (2)
Serious adverse reactions ^{e)}	0	0	0	0	0	0.5 (1)	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days after the study vaccination

b) Events occurring within 5 days after the study vaccination

c) Except for solicited adverse events occurring within 5 days after the study vaccination

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Events occurring during the study period

**Table 49. Incidences of solicited adverse events by age category
(Study 006 Cohorts 1, 2, and 3, safety analysis set)**

	50-64 years					≥65 years				
	Cohort 1		Cohort 2		Cohort 3	Cohort 1		Cohort 2		Cohort 3
	Capvaxive (N = 48)	PCV15 (N = 25)	Capvaxive (N = 80)	PPSV23 (N = 39)	Capvaxive (N = 17)	Capvaxive (N = 182)	PCV15 (N = 92)	Capvaxive (N = 94)	PPSV23 (N = 46)	Capvaxive (N = 88)
Solicited injection site reactions	47.9 (23)	56.0 (14)	52.5 (42)	64.1 (25)	47.1 (8)	37.9 (69)	45.7 (42)	35.1 (33)	45.7 (21)	43.2 (38)
Injection site erythema	10.4 (5)	12.0 (3)	6.3 (5)	15.4 (6)	11.8 (2)	6.6 (12)	6.5 (6)	8.5 (8)	4.3 (2)	6.8 (6)
Injection site pain	45.8 (22)	52.0 (13)	52.5 (42)	56.4 (22)	47.1 (8)	33.0 (60)	41.3 (38)	31.9 (30)	39.1 (18)	43.2 (38)
Injection site swelling	8.3 (4)	12.0 (3)	5.0 (4)	23.1 (9)	17.6 (3)	8.2 (15)	7.6 (7)	4.3 (4)	10.9 (5)	9.1 (8)
Solicited systemic reactions	20.8 (10)	28.0 (7)	22.5 (18)	30.8 (12)	23.5 (4)	20.9 (38)	19.6 (18)	28.7 (27)	17.4 (8)	25.0 (22)
Fatigue	14.6 (7)	24.0 (6)	13.8 (11)	20.5 (8)	17.6 (3)	14.3 (26)	15.2 (14)	23.4 (22)	6.5 (3)	22.7 (20)
Headache	12.5 (6)	12.0 (3)	12.5 (10)	17.9 (7)	17.6 (3)	5.5 (10)	8.7 (8)	8.5 (8)	6.5 (3)	6.8 (6)
Myalgia	12.5 (6)	0	13.8 (11)	15.4 (6)	23.5 (4)	6.0 (11)	3.3 (3)	6.4 (6)	4.3 (2)	5.7 (5)
Pyrexia	0	4.0 (1)	1.3 (1)	0	0	2.2 (4)	2.2 (2)	4.3 (4)	2.2 (1)	0

Incidence % (n)

Tables 50 and 51 show a summary of adverse events and solicited adverse events in the Japanese population in Cohorts 1 and 2. Although the number of Japanese participants was limited in both cohorts, the incidences of adverse events and adverse reactions in the Japanese population in Cohort 1 were generally similar between the vaccine groups or lower in the Capvaxive group, and they were similar to or lower than those in the overall population in either vaccine group. In Cohort 2, the incidences of adverse events and adverse reactions in the Capvaxive group in the Japanese population were lower than those in the overall population as well. All adverse events were mild (Grade 1) in Cohort 1 and mild (Grade 1) or moderate (Grade 2) in Cohort 2. Neither deaths nor serious adverse events occurred in either cohort. In Cohort 3, no Japanese subjects were enrolled.

Table 50. Summary of safety in the Japanese population (Study 006 Cohorts 1 and 2, safety analysis set)

	Cohort 1		Cohort 2	
	Capvaxive (N = 31)	PCV15 (N = 19)	Capvaxive (N = 11)	PPSV23 (N = 2)
All adverse events ^{a)}	38.7 (12)	47.4 (9)	18.2 (2)	100 (2)
Solicited adverse events ^{b)}	35.5 (11)	42.1 (8)	18.2 (2)	100 (2)
Solicited injection site reactions	25.8 (8)	42.1 (8)	9.1 (1)	100 (2)
Solicited systemic reactions	9.7 (3)	5.3 (1)	9.1 (1)	0
Non-solicited adverse events ^{a)c)}	9.7 (3)	10.5 (2)	0	100 (2)
All adverse reactions ^{a)}	32.3 (10)	42.1 (8)	18.2 (2)	100 (2)
Non-solicited adverse reactions ^{a)c)}	3.2 (1)	0	0	0
Grade ≥3 adverse events ^{a)d)}	0	0	0	0
Death ^{e)}	0	0	0	0
Serious adverse events ^{e)}	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days after the study vaccination

b) Events occurring within 5 days after the study vaccination

c) Except for solicited adverse events occurring within 5 days after the study vaccination

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Events occurring during the study period

**Table 51. Incidences of solicited adverse events in the Japanese population
(Study 006 Cohorts 1 and 2, safety analysis set)**

	Cohort 1		Cohort 2	
	Capvaxive (N = 31)	PCV15 (N = 19)	Capvaxive (N = 11)	PPSV23 (N = 2)
Solicited injection site reactions	25.8 (8)	42.1 (8)	9.1 (1)	100 (2)
Injection site erythema	0	0	0	50.0 (1)
Injection site pain	25.8 (8)	36.8 (7)	9.1 (1)	50.0 (1)
Injection site swelling	0	10.5 (2)	0	100 (2)
Solicited systemic reactions	9.7 (3)	5.3 (1)	9.1 (1)	0
Fatigue	9.7 (3)	5.3 (1)	9.1 (1)	0
Headache	0	5.3 (1)	0	0
Myalgia	0	0	0	0
Pyrexia	0	0	0	0

Incidence % (n)

(b) Safety in high-risk adults

Safety of Capvaxive in high-risk adults was evaluated based on results from Study 003 Cohort 1 and Studies 009, 007, and 008 as presented below. Safety of Capvaxive in high-risk adults regardless of prior pneumococcal vaccination history was similar to that of PPSV23 and PCV15, irrespective of the number and type of risk factors, and no safety concerns specific to Japanese participants were identified. Capvaxive is thus considered to have acceptable safety in this population.

Cohort 1 of foreign phase III study (Study 003)

In Study 003 Cohort 1 (adults aged ≥ 50 years), approximately 36% of participants had one or more prespecified risk factors for pneumococcal disease [see Section 7.R.1.2]. Tables 52 and 53 show a summary of adverse events and incidences of solicited adverse events, respectively, in the subgroup analysis by number of risk factors.

Table 52. Summary of adverse events (Study 003 Cohort 1, safety analysis set)

	Without risk factors		With 1 risk factor		With ≥ 2 risk factors	
	Capvaxive (N = 730)	PCV20 (N = 766)	Capvaxive (N = 347)	PCV20 (N = 328)	Capvaxive (N = 100)	PCV20 (N = 81)
All adverse events ^{a)}	59.9 (437)	68.5 (525)	54.2 (188)	63.4 (208)	60.0 (60)	55.6 (45)
Solicited adverse events ^{b)}	51.8 (378)	62.4 (478)	48.1 (167)	59.5 (195)	55.0 (55)	43.2 (35)
Solicited injection site reactions	43.0 (314)	56.8 (435)	38.6 (134)	50.3 (165)	39.0 (39)	37.0 (30)
Solicited systemic reactions	28.6 (209)	28.9 (221)	25.6 (89)	27.1 (89)	36.0 (36)	16.0 (13)
Non-solicited adverse events ^{a)c)}	21.5 (157)	24.5 (188)	20.2 (70)	15.2 (50)	24.0 (24)	17.3 (14)
All adverse reactions ^{a)}	52.6 (384)	62.9 (482)	49.0 (170)	60.1 (197)	55.0 (55)	44.4 (36)
Non-solicited adverse reactions ^{a)c)}	6.8 (50)	7.7 (59)	5.5 (19)	4.3 (14)	6.0 (6)	2.5 (2)
Grade ≥ 3 adverse events ^{a)d)}	1.9 (14)	3.0 (23)	1.7 (6)	3.7 (12)	7.0 (7)	6.2 (5)
Death ^{e)}	0.3 (2)	0.1 (1)	0.3 (1)	0	1.0 (1)	1.2 (1)
Serious adverse events ^{e)}	1.4 (10)	1.7 (13)	0.9 (3)	2.4 (8)	6.0 (6)	3.7 (3)
Serious adverse reactions ^{e)}	0	0	0	0	0	0
Adverse events leading to discontinuation ^{e)}	0	0	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days after the study vaccination

b) Events occurring within 5 days after the study vaccination

c) Except for solicited adverse events occurring within 5 days after the study vaccination

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Events occurring during the study period

Table 53. Incidences of solicited adverse events (Study 003 Cohort 1, safety analysis set)

	Without risk factors		With 1 risk factor		With ≥ 2 risk factors	
	Capvaxive (N = 730)	PCV20 (N = 766)	Capvaxive (N = 347)	PCV20 (N = 328)	Capvaxive (N = 100)	PCV20 (N = 81)
Solicited injection site reactions	43.0 (314)	56.8 (435)	38.6 (134)	50.3 (165)	39.0 (39)	37.0 (30)
Injection site erythema	5.6 (41)	7.2 (55)	5.2 (18)	4.9 (16)	5.0 (5)	3.7 (3)
Injection site pain	41.4 (302)	54.6 (418)	36.3 (126)	49.1 (161)	36.0 (36)	34.6 (28)
Injection site swelling	5.5 (40)	9.8 (75)	5.8 (20)	5.8 (19)	11.0 (11)	4.9 (4)
Solicited systemic reactions	28.6 (209)	28.9 (221)	25.6 (89)	27.1 (89)	36.0 (36)	16.0 (13)
Fatigue	19.5 (142)	21.1 (162)	19.0 (66)	18.9 (62)	29.0 (29)	7.4 (6)
Headache	11.5 (84)	12.7 (97)	10.4 (36)	14.0 (46)	15.0 (15)	11.1 (9)
Myalgia	6.0 (44)	7.3 (56)	4.3 (15)	6.7 (22)	11.0 (11)	1.2 (1)
Pyrexia	1.4 (10)	1.2 (9)	1.2 (4)	1.2 (4)	1.0 (1)	2.5 (2)

Incidence % (n)

The incidences of adverse events were similar across the subgroups and were comparable to those in the overall population, although the numbers of participants were unbalanced among the subgroups. Among solicited adverse events, the incidences of solicited systemic reactions differed by $>10\%$ between the subgroups with 1 risk factor and those with ≥ 2 risk factors. In particular, the incidence of fatigue differed by $\geq 10\%$ between these subgroups. However, all cases of fatigue in the subgroup with ≥ 2 risk factors were mild (Grade 1) or moderate (Grade 2) in severity, and most resolved within 3 days. No notable differences were observed in severity or duration compared with the subgroups with no risk factors or with 1 risk factor. In the subgroup with ≥ 2 risk factors, the incidence of solicited adverse events was slightly higher in the Capvaxive group than in the PCV20 group, and the incidences of solicited systemic reactions, particularly fatigue and myalgia, were higher in the Capvaxive group than in the PCV20 group. The differences in the incidences of solicited systemic reactions, particularly spontaneously reported events, may have been attributable to the markedly higher proportion of females in the Capvaxive group (53%) than in the PCV20 group (38.3%) in this subgroup. Capvaxive is thus considered to raise no safety concerns.

Global phase III study (Study 008)

The global phase III study (Study 008) included pneumococcal vaccine-naïve adults aged 18 to 64 years at risk of pneumococcal disease (with diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, or chronic lung disease). Table 54 shows a summary of adverse events in Study 008 [for participant characteristics about risk factors, see Section 7.R.1.2].

Table 54. Summary of adverse events (Study 008, safety analysis set)

	After the first dose		After the second dose	
	Capvaxive/saline (N = 386)	PCV15/PPSV23 (N = 130)	Capvaxive/saline (N = 374)	PCV15/PPSV23 (N = 128)
All adverse events ^{a)}	62.7 (242)	75.4 (98)	32.1 (120)	82.8 (106)
Solicited adverse events ^{b)}	58.5 (226)	70.8 (92)	24.9 (93)	81.3 (104)
Solicited injection site reactions	50.5 (195)	63.8 (83)	9.6 (36)	77.3 (99)
Solicited systemic reactions	32.9 (127)	30.8 (40)	20.6 (77)	43.0 (55)
Non-solicited adverse events ^{a)c)}	19.2 (74)	26.9 (35)	11.8 (44)	13.3 (17)
All adverse reactions ^{a)}	58.5 (226)	70.8 (92)	22.2 (83)	80.5 (103)
Non-solicited adverse reactions ^{a)c)}	5.2 (20)	3.1 (4)	0.8 (3)	2.3 (3)
Grade ≥ 3 adverse events ^{a)d)}	2.6 (10)	3.1 (4)	1.3 (5)	14.8 (19)
Death ^{e)}	0	0	0	0
Serious adverse events ^{e)}	1.8 (7)	3.1 (4)	0.8 (3)	2.3 (3)
Serious adverse reactions ^{e)}	0	0	0	0
Adverse events leading to discontinuation ^{e)}	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days postvaccination of each study vaccine (first or second dose)

b) Events occurring within 5 days postvaccination of each study vaccine (first or second dose)

c) Except for solicited adverse events occurring within 5 days postvaccination of each study vaccine (first or second dose)

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Period from the first dose to 8 weeks postvaccination (before the second dose) or from the second dose to the end of the study

Among solicited adverse events occurring within 5 days after each study vaccination, the incidence of solicited injection-site reactions was lower in the Capvaxive/saline group after the first dose than in the PCV15/PPSV23 group after the first and second doses. The incidence of solicited systemic reactions in the Capvaxive/saline group after the first dose was similar to that in the PCV15/PPSV23 group after the first dose and lower than that in the PCV15/PPSV23 group after the second dose. Most events in the Capvaxive/saline group after the first and second doses and in the PCV15/PPSV23 group after the first dose were mild (Grade 1), whereas events in the PCV15/PPSV23 group after the second dose were mild (Grade 1) or moderate (Grade 2). Severe (Grade 3) events occurred in 3 participants (0.8%) after the first dose and 1 participant (0.3%) after the second dose in the Capvaxive/saline group, and in the PCV15/PPSV23 group, 0 participants after the first dose and 17 participants (13.3%) after the second dose. A Grade 4 event occurred only in 1 participant (0.3%) in the Capvaxive/saline group after the second dose. Most events resolved within 3 days.

Of adverse events occurring within 30 days after the study vaccination, events reported in $\geq 5\%$ of participants in either group were solicited adverse events of injection site pain, injection site erythema, injection site swelling, fatigue, myalgia, and headache. Most of the events were mild (Grade 1) or moderate (Grade 2) in both groups. Of all severe (Grade 3) or higher adverse events, the incidences of Grade 3 and Grade 4 events in the Capvaxive/saline group were 1.3% (5 participants) and 1.3% (5 participants), respectively, after the first dose and 0.5% (2 participants) and 0.8% (3 participants), respectively, after the second dose. In the PCV15/PPSV23 group, the corresponding incidences were 0.8% (1 participant) and 2.3% (3 participants), respectively, after the first dose and 12.5% (16 participants) and 2.3% (3 participants), respectively, after the second dose. There were no Grade 4 adverse events occurring in more than 1 participant.

During the study period, neither deaths nor adverse events leading to study discontinuation occurred. Serious adverse events are as described in Section 7.3.4, and a causal relationship to the study vaccine was ruled out for all of them.

Table 55 shows a summary of adverse events by number of risk factors. The safety profiles were similar across the subgroups and were consistent with those observed in the overall population, although the numbers of participants were unbalanced among the subgroups. Safety profiles by type of risk factors were investigated and found to be consistent irrespective of type of risk factors. Safety profiles in subgroups by age (18-49 years and 50-64 years) were investigated and found to be similar to that in the overall population, although the incidence of adverse events tended to be higher in the subgroup aged 18 to 49 years than in the subgroup aged 50 to 64 years.

Table 55. Summary of adverse events by number of risk factors (Study 008, safety analysis set)

	With 1 risk factor		With ≥ 2 risk factors	
	Capvaxive/saline (N = 326)	PCV15/PPSV23 (N = 108)	Capvaxive/saline (N = 60)	PCV15/PPSV23 (N = 22)
All adverse events ^{a)}	70.2 (229)	89.8 (97)	60.0 (36)	95.5 (21)
Solicited adverse events ^{b)}	64.7 (211)	88.0 (95)	53.3 (32)	81.8 (18)
Solicited injection site reactions	53.1 (173)	83.3 (90)	50.0 (30)	77.3 (17)
Solicited systemic reactions	43.3 (141)	54.6 (59)	26.7 (16)	59.1 (13)
Non-solicited adverse events ^{a)c)}	24.5 (80)	36.1 (39)	26.7 (16)	22.7 (5)
All adverse reactions ^{a)}	63.8 (208)	87.0 (94)	55.0 (33)	81.8 (18)
Non-solicited adverse reactions ^{a)c)}	4.9 (16)	6.5 (7)	8.3 (5)	0
Grade ≥ 3 adverse events ^{a)d)}	4.0 (13)	14.8 (16)	3.3 (2)	31.8 (7)
Death ^{e)}	0	0	0	0
Serious adverse events ^{e)}	2.5 (8)	1.9 (2)	3.3 (2)	22.7 (5)
Serious adverse reactions ^{e)}	0	0	0	0
Adverse events leading to discontinuation ^{e)}	0	0	0	0

Incidence % (n)

- a) Events occurring within 30 days postvaccination of each study vaccine (first or second dose)
- b) Events occurring within 5 days postvaccination of each study vaccine (first or second dose)
- c) Except for solicited adverse events occurring within 5 days postvaccination of each study vaccine (first or second dose)
- d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).
- e) Period from the first dose to 8 weeks postvaccination (before the second dose) or from the second dose to the end of the study

Tables 56 and 57 show a safety summary and solicited adverse events in the Japanese population. The safety profile in the Japanese population was similar to that in the overall population. Incidences of all adverse events, all adverse reactions, and non-solicited adverse events in the Capvaxive/saline group after the first and second doses were similar to or lower than those in the PCV15/PPSV23 group for all events. The incidence of injection site swelling, a solicited adverse event, in the Capvaxive/saline group after the first dose was 12.9% (4 participants), which was higher than that in the PCV15/PPSV23 group (0 participants), but all of the events were mild (Grade 1) or moderate (Grade 2) and resolved within 3 days. A serious adverse event occurred in 1 participant in the Capvaxive/saline group after the second dose (sleep apnoea syndrome), but a causal relationship to the study vaccine was ruled out for the event. Neither deaths nor adverse events leading to discontinuation occurred in either group.

Table 56. Summary of adverse events in the Japanese population (Study 008, safety analysis set)

	After the first dose		After the second dose	
	Capvaxive/saline (N = 31)	PCV15/PPSV23 (N = 5)	Capvaxive/saline (N = 31)	PCV15/PPSV23 (N = 5)
All adverse events ^{a)}	54.8 (17)	100 (5)	16.1 (5)	100 (5)
Solicited adverse events ^{b)}	54.8 (17)	100 (5)	6.5 (2)	100 (5)
Solicited injection site reactions	48.4 (15)	100 (5)	0	100 (5)
Solicited systemic reactions	16.1 (5)	60.0 (3)	6.5 (2)	20.0 (1)
Non-solicited adverse events ^{a)c)}	9.7 (3)	20.0 (1)	9.7 (3)	40.0 (2)
All adverse reactions ^{a)}	54.8 (17)	100 (5)	6.5 (2)	100 (5)
Non-solicited adverse reactions ^{a)c)}	3.2 (1)	20.0 (1)	0	0
Grade ≥ 3 adverse events ^{a)d)}	0	0	3.2 (1)	0
Death ^{e)}	0	0	0	0
Serious adverse events ^{e)}	0	0	3.2 (1)	0
Adverse events leading to discontinuation ^{e)}	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days postvaccination of each study vaccine (first or second dose)

b) Events occurring within 5 days postvaccination of each study vaccine (first or second dose)

c) Except for solicited adverse events occurring within 5 days postvaccination of each study vaccine (first or second dose)

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Period from the first dose to 8 weeks postvaccination (before the second dose) or from the second dose to the end of the study

Table 57. Incidences of solicited adverse events in the Japanese population (Study 008, safety analysis set)

	After the first dose		After the second dose	
	Capvaxive/saline (N = 31)	PCV15/PPSV23 (N = 5)	Capvaxive/saline (N = 31)	PCV15/PPSV23 (N = 5)
Solicited injection site reactions	48.4 (15)	100 (5)	0	100 (5)
Injection site erythema	6.5 (2)	0	0	20.0 (1)
Injection site pain	48.4 (15)	100 (5)	0	100 (5)
Injection site swelling	12.9 (4)	0	0	40.0 (2)
Solicited systemic reactions	16.1 (5)	60.0 (3)	6.5 (2)	20.0 (1)
Fatigue	16.1 (5)	60.0 (3)	3.2 (1)	20.0 (1)
Headache	0	0	6.5 (2)	20.0 (1)
Myalgia	0	20.0 (1)	0	0
Pyrexia	0	0	0	20.0 (1)

Incidence % (n)

Foreign phase III study (Study 007)

Study 007 included adults with HIV infection aged ≥ 18 years regardless of prior pneumococcal vaccination history.³²⁾ Table 58 shows a summary of adverse events.

Table 58. Summary of adverse events (Study 007, safety analysis set)

	After the first dose		After the second dose	
	Capvaxive/saline (N = 155)	PCV15/PPSV23 (N = 155)	Capvaxive/saline (N = 153)	PCV15/PPSV23 (N = 151)
All adverse events ^{a)}	63.2 (98)	70.3 (109)	42.5 (65)	76.2 (115)
Solicited adverse events ^{b)}	56.1 (87)	66.5 (103)	28.8 (44)	72.8 (110)
Solicited injection site reactions	48.4 (75)	61.3 (95)	12.4 (19)	70.9 (107)
Solicited systemic reactions	31.6 (49)	29.0 (45)	22.9 (35)	29.8 (45)
Non-solicited adverse events ^{a)c)}	23.2 (36)	21.3 (33)	22.2 (34)	19.2 (29)
All adverse reactions ^{a)}	56.1 (87)	67.1 (104)	28.1 (43)	72.8 (110)
Non-solicited adverse reactions ^{a)c)}	5.2 (8)	3.2 (5)	1.3 (2)	2.6 (4)
Grade ≥ 3 adverse events ^{a)d)}	1.3 (2)	2.6 (4)	3.3 (5)	5.3 (8)
Death ^{e)}	0	0	0.7 (1)	0
Serious adverse events ^{e)}	0.6 (1)	1.3 (2)	2.6 (4)	2.6 (4)
Serious adverse reactions ^{e)}	0	0	0	0
Adverse events leading to discontinuation ^{e)}	0	0	0	0

Incidence % (n)

a) Events occurring within 30 days postvaccination of each study vaccine (first or second dose)

b) Events occurring within 5 days postvaccination of each study vaccine (first or second dose)

c) Except for solicited adverse events occurring within 5 days postvaccination of each study vaccine (first or second dose)

d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

e) Period from the first dose to 8 weeks postvaccination (before the second dose) or from the second dose to the end of the study

Among solicited adverse events occurring within 5 days after the study vaccination, the incidence of solicited injection site reactions was lower in the Capvaxive/saline group after the first dose than in the PCV15/PPSV23 group after the first and second doses. The incidence of solicited systemic reactions in the Capvaxive/saline group after the first dose was similar to the incidences in the PCV15/PPSV23 group after the first and second doses. Most of the events were mild (Grade 1) or moderate (Grade 2). Severe (Grade 3) solicited adverse events occurred in 1 participant (0.6%) after the first dose and 1 participant (0.7%) after the second dose in the Capvaxive/saline group, and in the PCV15/PPSV23 group 0 participants after the first dose and 4 participants (2.6%) after the second dose. A Grade 4 event occurred only in 1 participant (0.6%) in the PCV15/PPSV23 group after the first dose. Most events resolved within 3 days.

Of adverse events occurring within 30 days after the study vaccination, events reported in $\geq 5\%$ of participants in either group were mostly solicited adverse events of injection site pain, injection site erythema, injection site swelling, fatigue, myalgia, headache, and diarrhoea. In terms of severity, most of the events were mild (Grade 1) or moderate (Grade 2) in both groups. Of all severe (Grade 3) or higher adverse events, the incidences of Grade 3 and Grade 4 events in the Capvaxive/saline group were 0.6% (1 participant) and 0.6% (1 participant), respectively, after the first dose and 0.7% (1 participant) and 2.6% (4 participants), respectively, after the second dose. In the PCV15/PPSV23 group, the corresponding incidences were 0.6% (1 participant) and 1.9% (3 participants), respectively, after the first dose and 3.3% (5 participants) and 2.0% (3 participants), respectively, after the second dose. There were no Grade 4 adverse events occurring in more than 1 participant.

During the study period, an adverse event leading to death occurred in 1 participant in the Capvaxive/saline group (death of unknown cause³⁸⁾), but a causal relationship to the study vaccine was ruled out for the event. Serious adverse events are as described in Section 7.3.5, and a causal relationship to the study vaccine was ruled out for all of them. No adverse events leading to study discontinuation occurred.

Table 59 shows a summary of adverse events by CD4-positive T-cell count. The safety profile in each subgroup defined by count of CD4-positive T-cell count was similar to that in the overall population.

Table 59. Summary of adverse events by CD4-positive T-cell count (Study 007, safety analysis set)

	CD4-positive T-cell count ≥50 cells/μL and <500 cells/μL		CD4-positive T-cell count ≥500 cells/μL	
	Capvaxive/saline (N = 37)	PCV15/PPSV23 (N = 41)	Capvaxive/saline (N = 118)	PCV15/PPSV23 (N = 114)
All adverse events ^{a)}	64.9 (24)	90.2 (37)	73.7 (87)	91.2 (104)
Solicited adverse events ^{b)}	56.8 (21)	82.9 (34)	63.6 (75)	89.5 (102)
Solicited injection site reactions	45.9 (17)	80.5 (33)	52.5 (62)	85.1 (97)
Solicited systemic reactions	37.8 (14)	41.5 (17)	44.9 (53)	43.9 (50)
Non-solicited adverse events ^{a)c)}	40.5 (15)	29.3 (12)	37.3 (44)	37.7 (43)
All adverse reactions ^{a)}	56.8 (21)	82.9 (34)	63.6 (75)	89.5 (102)
Non-solicited adverse reactions ^{a)c)}	10.8 (4)	2.4 (1)	4.2 (5)	7.0 (8)
Grade ≥3 adverse events ^{a)d)}	10.8 (4)	2.4 (1)	1.7 (2)	8.8 (10)
Death ^{e)}	2.7 (1)	0	0	0
Serious adverse events ^{e)}	10.8 (4)	0	0	5.3 (6)
Serious events reactions ^{e)}	0	0	0	0
Adverse events leading to discontinuation ^{e)}	0	0	0	0

Incidence % (n)

- a) Events occurring within 30 days postvaccination of each study vaccine (first or second dose)
- b) Events occurring within 5 days postvaccination of each study vaccine (first or second dose)
- c) Except for solicited adverse events occurring within 5 days postvaccination of each study vaccine (first or second dose)
- d) Grading was performed according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).
- e) Period from the first dose to 8 weeks postvaccination (before the second dose) or from the second dose to the end of the study

In Study 007, the population can be divided into the following subgroups by prior vaccination status: The pneumococcal vaccine-naïve subgroup consisting of 100 participants in the Capvaxive/saline group and 98 participants in the PCV15/PPSV23 group; the subgroup with prior vaccination with PCV13 alone consisting of 18 participants in the Capvaxive/saline group and 18 participants in the PCV15/PPSV23 group; and the subgroup with prior vaccination with PPSV23 alone or PCV13/PPSV23 consisting of 37 participants in the Capvaxive/saline group and 39 participants in the PCV15/PPSV23 group. The incidences of adverse reactions and solicited adverse events in the subgroup with prior vaccination with PCV13 alone tended to be higher than those in the other subgroups. However, regardless of prior pneumococcal vaccination history, the safety profiles were similar to that in the overall population. The incidence of adverse reactions was 63.0% (63 participants) in the Capvaxive/saline group and 84.7% (83 participants) in the PCV15/PPSV23 group in the pneumococcal vaccine-naïve subgroup; 77.8% (14 participants) in the Capvaxive/saline group and 100% (18 participants) in the PCV15/PPSV23 group in the subgroup with prior vaccination with PCV13 alone; and 51.4% (19 participants) in the Capvaxive/saline group and 89.7% (35 participants) in the PCV15/PPSV23 group in the subgroup with prior vaccination with PPSV23 alone or PCV13/PPSV23. The incidence of solicited adverse events was 63.0% (63 participants) in the Capvaxive/saline group and 84.7% (83 participants) in the PCV15/PPSV23 group in the pneumococcal vaccine-naïve subgroup; 77.8% (14 participants) in the Capvaxive/saline group and 100% (18 participants) in the PCV15/PPSV23 group in the subgroup with prior vaccination with PCV13 alone; and 51.4% (19 participants) in the Capvaxive/saline group and 89.7% (35 participants) in the PCV15/PPSV23 group in the subgroup with prior vaccination with PPSV23 alone or PCV13/PPSV23.

(c) Foreign post-marketing safety information

Capvaxive was first approved for the indication of use in adults aged ≥ 18 years in the US on June 17, 2024. During the reporting period for the first periodic safety update report (PSUR) (June 17 to December 16, 2024), approximately [REDACTED] doses are estimated to have been administered. A total of 105 adverse events in 30 vaccine recipients were reported in the post-marketing setting for Capvaxive, of which 14 events in 5 vaccine recipients were serious. The most frequently reported adverse reactions were rash and pyrexia (5 events each), injection site pain, vaccination failure, and erythema (4 events each). The most commonly reported serious event was loss of consciousness (2 events); however, both events resolved, and there was insufficient information to support a causal relationship to Capvaxive. No new safety information potentially affecting the safety profile of Capvaxive has become available to date.

PMDA's view:

Based on results from Study 009, Study 003 Cohort 1, and Studies 006, 008, and 007, the points listed below were confirmed. Capvaxive is found to have no critical safety concerns in adults aged ≥ 50 years and high-risk adults, has a safety profile similar to that of existing pneumococcal vaccines (PPSV23, PCV15, and PCV20), and is thus considered to have acceptable safety. Nevertheless, given the limited experience with Capvaxive in Japanese individuals, the applicant should continue collecting safety information. If any new safety concerns are identified, relevant information should be promptly provided to healthcare professionals, and appropriate measures, including establishment of safety specification and revision of the package insert, should be considered as necessary based on the information obtained.

- Although adverse events occurred in approximately half of Capvaxive recipients, most of them were solicited local or systemic adverse events commonly observed with the other vaccinations and mild (Grade 1) or moderate (Grade 2). In addition, most solicited adverse events resolved within 3 days.
- Most adverse events observed after Capvaxive vaccination occurred at incidences similar to those observed in the control groups (PPSV23, PCV20, PCV15, and PCV15/PPSV23 groups).
- Adverse events leading to death occurred after Capvaxive vaccination in Study 003 Cohort 1 and Study 007, but their incidence was low and similar to that in the control groups (PCV20 or PCV15/PPSV23 groups), and a causal relationship to the study vaccine was ruled out for all of them.
- After Capvaxive vaccination, serious adverse events occurred, but their incidence was low and similar to that in the control groups (PPSV23, PCV20, PCV15, or PCV15/PPSV23 groups). The serious adverse reaction was limited to injection site cellulitis in the Capvaxive group in Study 006. The reaction resolved without sequelae following antimicrobial treatment at Day 16 postvaccination and thus is considered as an event associated with study vaccination procedure.
- No safety concerns specific to age, number or type of risk factors, or status of prior pneumococcal vaccination have been identified. No safety concerns specific to Japanese individuals have been identified either.

7.R.3 Clinical positioning and indication

The applicant's explanation about the clinical positioning and indication of Capvaxive:

Pneumonia is one of the leading causes of death in Japan (FY2023 Vital Statistics <https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450011&tstat=000001028897&cycle=7&year=20230>

&month=0&tclass1=000001053058&tclass2=000001053061&tclass3=000001053065&result_back=1
&cycle_facet=tclass1%3Atclass2%3Atclass3&tclass4val=0 [last accessed on May 23, 2023]). *Streptococcus pneumoniae* is the primary pathogenic bacterium of pneumonia (*BMC Infect Dis.* 2014;14:534, *Am J Respir Crit Care Med.* 2013;188:985-95). In addition, IPDs caused by *Streptococcus pneumoniae* such as meningitis and bacteraemia are extensively prevalent and highly fatal especially in the elderly, individuals with certain underlying diseases, and immunocompromised individuals (*BMJ Open.* 2018;8:e018553, *J Infect.* 2012;65:17-24, *J Infect Chemother.* 2021;27:1311-8). In the concerned susceptible population, preventive measures against pneumococcal disease are critical.

In Japan, PPSV23, PCV15, and PCV20 are approved as preventive vaccines against pneumococcal disease. PPSV23 is a pneumococcal polysaccharide vaccine covering 23 serotypes and has been included in the routine immunization program for the elderly since 2014. PCV15 and PCV20 are pneumococcal conjugate vaccines that cover 15 and 20 serotypes, respectively. By conjugating PnPs to CRM₁₉₇, a T-cell-dependent antigen, these vaccines induce a T-cell-dependent immune response and the generation of memory B cells, resulting in immunogenicity profiles different from that of PPSV23. Even in infants with immature immunocompetence, they can induce an immune response and thus have been adopted in a routine immunization program for children since 2024 (PCV13 was adopted in the routine immunization program for children from 2013 to 2024). Although PCV15 and PCV20 have not been adopted in the routine immunization program for the elderly, sequential vaccination with PCV15-PPSV23 and single vaccination with PCV20 in addition to the routine immunization with PPSV23 according to individual risk are recommended for high-risk adults (“Guidance for pneumococcal vaccination in high-risk individuals aged 6 to 64 years” Version 3, April 2025 by the Joint Committee of the Respiratory Vaccine Committee, the Japanese Respiratory Society/the Committee of Vaccines, the Japanese Association for Infectious Diseases/the Japanese Society for Vaccinology).

The introduction of routine immunization with PCV13 for children substantially reduced the incidence of IPD caused by vaccine serotypes in Japan (*Infectious Agents Surveillance Report.* 2023;44:11-12). As an indirect effect, the incidence of IPD caused by vaccine serotypes also decreased among adults (*Vaccine.* 2022;40:3338-44). However, according to Adult IPD Surveillance in Japan (Research for Enhanced Invasive Bacterial Infection Surveillance in Adults FY 2022-2024, Epidemiological Information on Invasive Pneumococcal Disease in Children and Adults (in Japanese), Project for Policy Research on Emerging and Re-emerging Infectious Diseases and Immunization, Health, Labour and Welfare Scientific Research Grants), although the proportions of IPD cases caused by serotypes included in approved pneumococcal vaccines have tended to decrease, a substantial disease burden due to the remaining serotypes, particularly serotypes 3, 19A, and 22F, persists.⁴¹⁾ Furthermore, the incidence of IPD caused by serotypes not included in approved pneumococcal vaccines, particularly serotypes 35B, 15A, and 23A, has tended to increase. Among the serotypes not included in approved pneumococcal vaccines, IPD caused by serotypes 35B, 15A, and 23A has been reported to be associated with poor outcomes and tends to show high rates of penicillin resistance (*J Infect Chemother.* 2021;27:1311-8, *J Infect Public Health.* 2020;13:1094-1100, etc.). In general, increasing antimicrobial resistance in *Streptococcus pneumoniae* is considered to contribute to treatment failure and increased mortality and

⁴¹⁾ According to the Adult IPD Surveillance in Japan, proportions of the serotypes included in PCV13, PCV15, PCV20, and PPSV23 changed from 45% to 26%, from 56% to 30%, from 69% to 45%, and from 67% to 45%, respectively, over a period between 2014 and 2023.

healthcare costs (*J Infect.* 2020;81:557-66, *J Infect Public Health.* 2020;13:1094-100). Therefore, new preventive strategies based on the epidemiology in adults are considered necessary. Unlike approved PCVs, which were developed primarily for the prevention of pneumococcal disease in children, Capvaxive is a PCV specifically designed for adults and is intended to address the major serotypes currently responsible for pneumococcal disease, based on the epidemiology of pneumococcal disease in adults in the context of pediatric PCV use. Capvaxive covers 8 additional serotypes not included in any approved pneumococcal vaccine (e.g., 35B, 15A, and 23A), as well as serotypes included in approved pneumococcal vaccines that still remain prevalent (e.g., 3, 19A, and 22F). Capvaxive has consistently covered approximately 80% of pneumococcal serotypes causing adult IPD identified through Adult IPD Surveillance since 2014. Therefore, introduction of Capvaxive in Japan is expected to provide a clinically meaningful improvement over the current situation in the prevention of pneumococcal disease in adults.

Although pneumococcal vaccines approved in Japan (PPSV23, PCV20, and PCV15) are not indicated for use in healthy adults aged 50 to 64 years, the risk for pneumococcal disease increases with age in adults aged ≥ 50 years (“Notification Status of Invasive Pneumococcal Disease Cases from Week 1 of 2014 to Week 35 of 2021 (in Japanese)” dated October 20, 2021, issued by the Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases; *Emerg Infect Dis.* 2018;24:2010-20, etc.). Because a substantial disease burden exists in adults aged 50 to 64 years, as in those aged ≥ 65 years, the applicant considered it meaningful, for expanding the prevention of pneumococcal disease among adults in Japan, to extend the indicated age population for Capvaxive to include healthy adults aged ≥ 50 years and thereby provide this population with access to vaccination. Therefore, the applicant considered it appropriate that the target population for Capvaxive should include not only adults aged ≥ 65 years and high-risk adults aged ≥ 18 years, but also healthy adults aged 50 to 64 years.

Based on the reviews in Sections 7.R.1 and 7.R.2, Capvaxive is expected to prevent pneumococcal disease caused by the 21 serotypes included in the vaccine and the cross-reactive serotype 15B in adults aged ≥ 50 years and high-risk adults aged ≥ 18 years. No major safety concerns were identified, and the safety profile is considered acceptable. Although clinical studies of Capvaxive did not include adults with congenital or acquired asplenia, sickle cell disease, haemoglobinopathies, or impaired host defense due to anatomical conditions such as cochlear implants and chronic cerebrospinal fluid leaks, pneumococcal vaccination is recommended for individuals with these diseases or conditions in Japanese and international guidelines.⁴²⁾ Therefore, the applicant considered it appropriate, as with approved pneumococcal vaccines, to include these diseases and conditions in the Precautions Concerning Indications section as conditions considered to place individuals at high risk for pneumococcal disease. These diseases or conditions are not widely prevalent, and thus enrollment of the evaluable number of participants with these diseases or conditions during a study period was difficult, but they are assumed to have immunological conditions similar to those of the participants included in the global phase III study (Study 008) and foreign phase III study (Study 007). In view of results from the clinical studies,

⁴²⁾ “Guidance for pneumococcal vaccination in high-risk individuals aged 6 to 64 years” Version 3, April 2025 by the Joint Committee of the Vaccine Working Group, Scientific Assembly of Infections and Tuberculosis, the Japanese Respiratory Society/the Committee of Vaccines, the Japanese Association for Infectious Diseases/the Japanese Society for Vaccinology. *Morb Mortal Wkly Rep.* 2025;74:1-8

Capvaxive can be expected to have favorable tolerability and efficacy in individuals with these diseases or conditions as well.

As described above, Capvaxive can address unmet medical needs that remain in adults aged ≥ 50 years and high-risk adults and thus is expected to offer a new option potentially replacing approved pneumococcal conjugate vaccines. The applicant considers it appropriate that the proposed indication for Capvaxive be defined as “prevention of disease caused by infection with *Streptococcus pneumoniae* (serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) in adults aged ≥ 50 years and in adults who are considered to be at increased risk for pneumococcal disease.” The applicant also considers it appropriate that the Precautions Concerning Indications section specify conditions considered to place individuals at high risk for pneumococcal disease, as with approved pneumococcal vaccines.

PMDA’s view:

Capvaxive is a PCV specifically designed for adults and is intended to address the major serotypes currently responsible for pneumococcal disease, based on the epidemiology of pneumococcal disease in adults in the context of pediatric PCV use. It covers 8 additional serotypes not included in any approved pneumococcal vaccine, including the increasingly prevalent and highly invasive serotypes 35B, 15A, and 23A, as well as serotypes included in approved pneumococcal vaccines that remain prevalent, including serotypes 3, 19A, and 22F. The applicant's view that Capvaxive would have clinical significance for the prevention of pneumococcal disease in adults in Japan is understandable.

The following applicant’s view on the efficacy and safety of Capvaxive is acceptable: Based on the reviews in Sections 7.R.1 and 7.R.2, Capvaxive can be expected to prevent pneumococcal disease caused by the 21 serotypes included in the vaccine and the cross-reactive serotype 15B in adults aged ≥ 65 years and high-risk adults aged ≥ 18 years, and no major safety concerns were identified; therefore, the safety profile is considered acceptable. In addition, although adults with congenital or acquired asplenia, sickle cell disease, haemoglobinopathies, or impaired host defense due to anatomical conditions such as cochlear implants and chronic cerebrospinal fluid leaks were not included in clinical studies of Capvaxive, pneumococcal vaccination is recommended for individuals with these diseases or conditions in Japanese and international guidelines. Considering the rarity of these diseases or conditions, it is considered appropriate that, as with approved pneumococcal vaccines, the Precautions Concerning Indications section specify these diseases and conditions as conditions considered to place individuals at high risk for pneumococcal disease.

On the other hand, the review in Section 7.R.1 has confirmed that Capvaxive induces an immune response in healthy adults aged 50 to 64 years, but whether Capvaxive would provide this population with efficacy as demonstrated in adults aged ≥ 65 years and high-risk adults remains unclear, because the existing pneumococcal vaccines (PPSV23, PCV15, and PCV20) used as control vaccines have not been approved for the indication in healthy adults aged < 65 years in Japan. The applicant’s explanation that a risk of pneumococcal disease in adults aged ≥ 50 years increases with age is understandable, but the risk of pneumococcal disease in healthy adults aged 50 to 64 years tends to be lower than that in high-risk adults and adults aged ≥ 65 years (*BMJ Open*. 2018;8:e018553, *Int J Infect Dis*. 2022;116:216-

22), and most of the adults aged 50 to 64 years affected by pneumococcal disease are classified as high-risk individuals (“Guidance for pneumococcal vaccination in high-risk individuals aged 6 to 64 years” Version 3, April 2025 by the Joint Committee of the Respiratory Vaccine Committee, the Japanese Respiratory Society/the Committee of Vaccines, the Japanese Association for Infectious Diseases/the Japanese Society for Vaccinology). Furthermore, the medical needs for prevention against pneumococcal disease in healthy adults aged 50 to 64 years in Japan are not clear, and a vaccination rate in the current routine immunization program (category B diseases) with PPSV23 in the elderly aged 65 years and high-risk adults aged 60 to 64 years is low. In view of the above situations, PMDA does not consider it definitely meaningful to include healthy adults aged 50 to 64 years in the eligible population. PMDA thus considers that healthy adults aged 50 to 64 years should not be included in the population eligible for Capvaxive.

Considering that inclusion of the serotypes for which efficacy of Capvaxive is expected in the Indication section is unlikely to provide meaningful information to healthcare professionals, it is appropriate to remove all serotypes from the Indication section and to describe them in the Precautions Concerning Indications section.

In view of the above review and labeling of existing pneumococcal vaccines (PPSV23, PCV15, and PCV20), the Indication and Precautions Concerning Indications sections should be specified as follows:

Indication

Prevention of disease caused by infection with *Streptococcus pneumoniae* in the elderly and in adults who are considered to be at increased risk for pneumococcal disease

Precautions Concerning Indications

- Capvaxive is not expected to prevent infections caused by pneumococcal serotypes other than 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B, or infections caused by pathogens other than *Streptococcus pneumoniae*.
- Capvaxive cannot be used for immunization against diphtheria.
- Adults who are considered to be at increased risk for pneumococcal disease refer to those with the following conditions:
 - Chronic heart disease, lung disease, liver disease, or kidney disease
 - Diabetes mellitus
 - Immunocompromised condition, or a suspected immunocompromised condition, because of an underlying disease or treatment
 - Congenital or acquired asplenia
 - Sickle cell disease or other haemoglobinopathies
 - Impaired host defense due to anatomical conditions such as cochlear implants or chronic cerebrospinal fluid leaks
 - Other conditions for which a physician considers vaccination with Capvaxive necessary

7.R.4 Dosage and administration

7.R.4.1 Dosage and administration

The applicant's explanation about the proposed dosage and administration:

The phase II part of the foreign phase I/II study in healthy adults (Study 001) [see Section 7.2] showed that Capvaxive has a safety profile similar to that of PPSV23 and suggested that it induces a functional OPA immune response associated with prevention of pneumococcal disease. Then, phase III studies were conducted using a dosage regimen similar to that in Study 001. While Study 001 used a vaccine product containing polysaccharides for each serotype at 4 µg/1.0 mL, phase III studies used a reformulated vaccine product containing polysaccharides for each serotype at 4 µg/0.5 mL. Reviews in Sections 7.R.1 and 7.R.2 confirmed that Capvaxive induces an immune response in adults aged ≥50 years and high-risk adults and has a safety profile similar to that of existing pneumococcal vaccines (PPSV23, PCV20, and PCV15).

Based on the above, the applicant considers that the Dosage and Administration of Capvaxive may be specified as "A single dose of 0.5 mL should be injected intramuscularly."

PMDA's view:

As described in Section 7.R.3, the target population of Capvaxive should be adults aged ≥65 years and high-risk adults. The Dosage and Administration of Capvaxive may be specified as "A single dose of 0.5 mL should be injected intramuscularly," based on clinical study results on immunogenicity and safety of Capvaxive in adults aged ≥65 years and high-risk adults, in which immune responses comparable to those induced by existing pneumococcal vaccines (PPSV23, PCV20, and PCV15) were confirmed and no particular safety concerns were identified.

7.R.4.2 Simultaneous vaccination with Capvaxive and other vaccines

The applicant's explanation about simultaneous vaccination with Capvaxive and other vaccines:

In a foreign phase III study (Study 005) in adults aged ≥50 years, immunogenicity and safety of simultaneous vaccination with Capvaxive and seasonal inactivated influenza vaccine (SIIV) (quadrivalent influenza vaccine) were evaluated.

In this study, participants in the simultaneous vaccination group received Capvaxive and SIIV by intramuscular injection and, 29 days later, received saline by intramuscular injection. Participants in the non-simultaneous vaccination group received SIIV and saline by intramuscular injection and, 29 days later, received Capvaxive by intramuscular injection. Capvaxive⁹⁾ and saline were administered at a dose of 0.5 mL each, and SIIV was administered at the recommended dose.

Of the 1,080 randomized participants (540 in the simultaneous vaccination group and 540 in the non-simultaneous vaccination group), 1,072 participants (536 in the simultaneous vaccination group and 536 in the non-simultaneous vaccination group) received at least one dose of the study vaccine, and 1,069 participants were included in the safety analysis set, excluding 3 participants.⁴³⁾ Among all randomized participants, those without protocol deviations that could have a significant impact on immunogenicity

⁴³⁾ They were excluded because it remained unclear whether Capvaxive or saline had been administered at Visit 1 (2 participants in the simultaneous vaccination group and 1 participant in the non-simultaneous vaccination group).

evaluation were defined as the PP population. For the analysis of serotype-specific OPA antibody titers at Day 30 postvaccination of Capvaxive vaccination, the PP population comprised 1,024 participants (525 in the simultaneous vaccination group and 499 in the non-simultaneous vaccination group). For the analysis of strain-specific hemagglutination inhibition (HAI) antibody titers at Day 30 after SIIV vaccination, the PP population comprised 1,052 participants (526 in the simultaneous vaccination group and 526 in the non-simultaneous vaccination group). These PP populations were used as the primary immunogenicity analysis sets.

The primary immunogenicity endpoint for Capvaxive was “serotype-specific OPA GMTs at Day 30 postvaccination of Capvaxive.” For demonstration of non-inferiority of simultaneous vaccination to non-simultaneous vaccination, the lower bound of the two-sided 95% CI of the GMR of serotype-specific OPA GMTs at Day 30 postvaccination of Capvaxive in the simultaneous vaccination group to that in the non-simultaneous vaccination group was required to exceed 0.50. The primary immunogenicity endpoint for SIIV was “strain-specific HAI GMT at Day 30 postvaccination of SIIV.” For demonstration of non-inferiority of simultaneous vaccination to non-simultaneous vaccination, the lower bound of the two-sided 95% CI of the GMR of strain-specific HAI GMT at Day 30 postvaccination of SIIV in the simultaneous vaccination group to that in the non-simultaneous vaccination group was required to exceed 0.67. Achievement of the primary immunogenicity objective required that all of the above non-inferiority criteria be met.

For immunogenicity, the serotype-specific OPA GMRs ranged from 0.56 (serotype 23B) to 0.84 (serotypes 3 and 33F). For 20 of 21 serotypes (excluding serotype 23B), the lower bound of the two-sided 95% CI of OPA GMR exceeded 0.5, but for serotype 23B, the lower bound of the two-sided 95% CI was 0.44. OPA GMFR for serotype 23B (ratio of OPA antibody titer at Day 30 postvaccination of Capvaxive to that at baseline) was 42.9 in the simultaneous vaccination group and 60.9 in the non-simultaneous vaccination group, and the OPA responder rate at Day 30 postvaccination of Capvaxive based on changes from baseline was as high as 83.0% in the simultaneous vaccination group and 84.7% in the non-simultaneous vaccination group. Strain-specific HAI GMRs ranged from 0.79 (A/H3N2 subtype) to 0.89 (B/Yamagata lineage). For 3 of 4 strains (excluding A/H3N2 subtype),⁴⁴⁾ the lower bound of the two-sided 95% CI of HAI GMR exceeded 0.67, but for A/H3N2 subtype, the lower bound of the two-sided 95% CI was 0.67. For A/H3N2 subtype, a proportion of participants with the HAI antibody titer at Day 29 postvaccination of SIIV being at least 1:40 was 84.2% in the simultaneous vaccination group and 85.5% in the non-simultaneous vaccination group, and the HAI GMFR (ratio of HAI antibody titer at Day 30 postvaccination of SIIV to that at baseline) was 5.6 in the simultaneous vaccination group and 7.1 in the non-simultaneous vaccination group. In view of the above findings, although the non-inferiority criteria were not met for certain serotypes and strains, simultaneous vaccination can still be expected to provide sufficient vaccine efficacy.

Table 60 shows incidences of solicited adverse reactions (injection site reactions and systemic reactions) within 5 days after the study vaccination. The incidence of solicited adverse reactions after simultaneous vaccination of Capvaxive and SIIV was similar to that after administration of Capvaxive alone. Most of

⁴⁴⁾ A/H1N1 subtype, A/H3N2 subtype, B/Yamagata lineage, B/Victoria lineage

the reactions were mild or moderate. Of adverse events within 30 days after the study vaccination, the incidence after simultaneous vaccination of Capvaxive and SIIV was similar to that after administration of Capvaxive or SIIV alone.

Table 60. Incidences of solicited injection site reactions and solicited systemic reactions within 5 days after the study vaccination (Study 005, safety analysis set)

	Simultaneous vaccination		Non-simultaneous vaccination	
	After simultaneous vaccination of Capvaxive + SIIV	After administration of saline	After simultaneous vaccination of saline + SIIV	After administration of Capvaxive
Solicited injection site reactions ^{a)}	52.2 (279/534)	7.5 (39/522)	12.7 (68/535)	48.3 (250/518)
Solicited systemic reactions	35.6 (190/534)	15.1 (79/522)	28.2 (151/535)	27.6 (143/518)

Incidence % (number of participants with events/number of participants analyzed)

a) Injection site reactions occurring on the arm with Capvaxive or saline administered

Adverse events leading to death occurred in 3 participants (1 participant in the simultaneous vaccination group [metastatic malignant melanoma⁴⁵⁾], 2 participants in the non-simultaneous vaccination group [septic shock⁴⁶⁾ and victim of homicide⁴⁷⁾ in 1 participant each]), but a causal relationship to the study vaccine was ruled out for all of them.

In view of the above results, the applicant considers simultaneous vaccination of Capvaxive and influenza vaccine possible. The Precautions Concerning Dosage and Administration section should state that other vaccines may be administered concomitantly if considered necessary by a physician.

PMDA accepted the applicant's explanation.

7.R.5 Post-marketing investigations

The applicant's explanation about post-marketing investigations of Capvaxive:

Results from Japanese and foreign clinical studies of Capvaxive show that common adverse reactions associated with Capvaxive include injection site pain, headache, fatigue, myalgia, and pyrexia, and the tolerability of Capvaxive is favorable [see Section 7.R.2]. Adverse events occurring after Capvaxive vaccination in clinical studies are similar to those occurring with control vaccines (PPSV23, PCV20, and PCV15), raising no safety concerns specific to Capvaxive [see Section 7.R.2].

⁴⁵⁾ 81-year-old woman. She had a medical history of constipation, drug hypersensitivity, headache, hypothyroidism, back pain, scoliosis, cardiac murmur, hyperlipidaemia, aortic arteriosclerosis, pulmonary hypertension, poor dental condition, asthenia, malignant melanoma, and osteoarthritis. She received SIIV and Capvaxive concomitantly. On Day 17 after the study vaccination (SIIV and Capvaxive), she experienced tarry stool, lassitude, weakness, and nausea and visited the emergency department. On the same day, she was admitted to the hospital with diagnoses of gastric ulcer bleeding, acute blood loss anaemia, and hypokalaemia. On Day 21, hypokalaemia improved (2.5 mmol/L). On Day 22, a decreased blood potassium level was found (2.0 mmol/L). Gastric ulcer bleeding and pulmonary hypertension resolved. She was discharged from the hospital with diagnoses of acute blood loss anaemia and gastrointestinal bleeding. On Day 23, a diagnosis of gastric ulcer was given. On Day 28, she was admitted to the hospital. Hypokalaemia was worsened by long-term diuretic therapy for pulmonary hypertension. Hypokalaemia and hypomagnesaemia owing to diarrhoea, gastric ulcer haemorrhage, and *H. pylori* infection were found. On Day 29, the blood potassium level was found within the normal range. Hypomagnesaemia resolved. She was discharged from the hospital with a diagnosis of hypokalaemia. The second dose of study vaccine was not administered because of blood loss anaemia. On Day 67, Helicobacter infection resolved. On Day 211, she died of metastatic malignant melanoma. Gastric ulcer, blood loss anaemia, hypokalaemia, and hyponatraemia resolved. Of note, a causal relationship to the study vaccine was ruled out for the metastatic malignant melanoma.

⁴⁶⁾ 61-year-old man. He received SIIV and Capvaxive in a non-concomitant manner. On Day 25 after the study vaccination (Capvaxive), he experienced chest pain, dyspnoea, and malaise and visited the emergency department. He experienced refractory multiple organ failure requiring endotracheal intubation, vasopressors, and cardiac stimulants and was diagnosed with septic shock. On the following day, he died. A causal relationship to the study vaccine was ruled out.

⁴⁷⁾ 61-year-old man. He received SIIV and Capvaxive in a non-concomitant manner. On Day 163 after the study vaccination (Capvaxive), he was reported as [REDACTED]. A causal relationship to the study vaccine was ruled out.

For Capvaxive, “severe allergic reactions (shock, anaphylaxis, etc.)” was specified as an important identified risk. In the clinical studies of Capvaxive, the applicable event was limited to bronchospasm in 1 participant in the Capvaxive group in Study 005, and the frequency is considered to be very low. Therefore, it would be difficult to collect sufficient information through post-marketing surveillance conducted in only a limited number of facilities or vaccine recipients. Routine pharmacovigilance activities, including collection of adverse reaction reports from Japan and overseas and literature surveillance, are considered a more appropriate means of actively collecting broad safety information without restricting the target population. Based on the above, the applicant considers it unnecessary to plan additional pharmacovigilance activities such as post-marketing surveillance. However, based on information collected and evaluated through early post-marketing phase vigilance and routine pharmacovigilance activities, the applicant will re-evaluate the need for additional pharmacovigilance activities or additional risk minimization activities if further evaluation of safety issues becomes necessary in the future.

PMDA’s view:

Results from the clinical studies of Capvaxive indicate that Capvaxive has a safety profile similar to that of PPSV23, PCV20, and PCV15, and to date, no safety concerns specific to Capvaxive have been identified [see Section 7.R.2]. The applicant’s explanation is understandable that severe allergic reactions (shock, anaphylaxis, etc.), which were established as a safety specification, are expected to occur infrequently in clinical practice and that, from a feasibility perspective, it would be difficult to collect relevant information through post-marketing surveillance conducted in only a limited number of facilities or vaccine recipients. However, the applicant should continue collecting and evaluating information on the safety of Capvaxive in all individuals eligible for Capvaxive, because the baseline characteristics such as comorbidities and medical history of high-risk adults evaluated in the clinical studies of Capvaxive are limited. Therefore, the applicant should collect information extensively via routine pharmacovigilance activities and, if new safety concerns regarding Capvaxive are identified, consider additional pharmacovigilance activities, including whether post-marketing surveillance is necessary, as well as additional risk minimization activities.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA’s conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA’s conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.8 and 5.3.5.1.9) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA

concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Capvaxive has efficacy in the prevention of disease caused by infection with *Streptococcus pneumoniae* in the elderly and in adults who are considered to be at increased risk for pneumococcal disease, and that Capvaxive has acceptable safety in view of its benefits. Capvaxive is clinically meaningful because it contains 21 serotypes of PnPs and offers a new option of pneumococcal vaccine.

The vaccine product and its active substance are both classified as powerful drugs.

PMDA has concluded that Capvaxive may be approved if Capvaxive is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 2, 2025

Product Submitted for Approval

Brand Name	Capvaxive for Intramuscular Injection Syringes
Non-proprietary Name	Pneumococcal 21-valent Conjugate Vaccine (Conjugate with a Non Toxic Variant of Diphtheria Toxin)
Applicant	MSD K.K.
Date of Application	November 8, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in the Review Report (1) (Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.3 Clinical positioning and indication," and "7.R.4 Dosage and administration").

PMDA also discussed the following points and took action as necessary.

1.1 Risk management plan (draft)

At the Expert Discussion, in addition to comments supporting PMDA's conclusion in "7.R.5 Post-marketing investigations" in the Review Report (1), the following comment was presented.

- Because evaluation of the vaccine efficacy of Capvaxive in the prevention of pneumococcal disease is important, information should be provided to healthcare professionals once results become available from the ongoing foreign phase III study (Study V116-010) and the planned real-world observational study using a test-negative case-control design [see Section 7.R.1.3].

PMDA has concluded that the risk management plan (draft) for Capvaxive should include the safety specification presented in Table 61, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 62, including activities for disseminating information in response to the review in "7.R.5 Post-marketing investigations" in the

Review Report (1) and the discussion at the Expert Discussion. PMDA asked the applicant to collect information on the duration of efficacy of Capvaxive and changes in the distribution of serotypes causing pneumococcal disease following the introduction of Capvaxive, using not only the ongoing foreign phase III study and the planned observational study but also epidemiological surveillance and published literature, and to provide the resulting findings to healthcare professionals. The applicant agreed.

Table 61. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Severe allergic reactions (shock, anaphylaxis, etc.)	Not applicable	Not applicable
Efficacy specification		
Not applicable		

Table 62. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Dissemination of information obtained through early post-marketing phase vigilance

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. Since the product is categorized as a drug with a new active ingredient, the re-examination period is 8 years.

Indication

Prevention of disease caused by infection with *Streptococcus pneumoniae* in the elderly and in adults who are considered to be at increased risk for pneumococcal disease

Dosage and Administration

A single dose of 0.5 mL should be injected intramuscularly.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

List of Abbreviations

Capvaxive	Capvaxive for Intramuscular Injection Syringes
CFU	Colony-forming unit
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CRM ₁₉₇	Cross reactive material 197
deOAc15B	De-O-acetylated polysaccharide from serotype 15B
DMSO	Dimethyl sulfoxide
ECL	Electrochemiluminescent
ELISA	Enzyme linked immunosorbent assay
FDA	Food and Drug Administration
HAI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HPSEC	High performance size exclusion chromatography
IPD	Invasive pneumococcal disease
LDA	Longitudinal data analysis
LIVCA cells	Cells at the limit of in vitro cell age
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
MOPA	Multiplexed opsonophagocytic activity assay
OPA	Opsonophagocytic activity
PBS	Phosphate buffered saline
PCV	Pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PCV15	15-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PMDA	Pharmaceuticals and Medical Devices Agency
PnPs	Pneumococcal capsular polysaccharide
PPSV23	23-valent pneumococcal polysaccharide vaccine
SIIV	Seasonal inactivated influenza vaccine
Th1	T helper (cell), type 1
Th2	T helper (cell), type 2
V116	A vaccine containing PnPs-CRM ₁₉₇ conjugates from 21 serotypes (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B)
WCB	Working cell bank
WHO	World Health Organization