Summary of Product Characteristic

1. NAME OF THE MEDICINAL PRODUCT

Generic Name: Recombinant Human Papillomavirus 9-Valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Vaccine *(Escherichia coli*)
Trade Name: Cecolin 9 PFS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cecolin 9 PFS is a mixture of nine aluminum hydroxide adjuvant-adsorbed recombinant L1 capsid proteins of human papillomavirus (HPV) type-6, type-11, type-16, type-18, type-31, type-33, type-45, type-52 and type-58 each self-assembled into virus-like particles (VLPs). The HPV-6, HPV11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58 L1 antigens are expressed in *Escherichia coli* by recombinant DNA technology.

Active Substance:
Each dose (0.5mL) contains:

Recombinant Human Papillomavirus Type 6 L1 protein	30μg
Recombinant Human Papillomavirus Type 11 L1 protein	40μg
Recombinant Human Papillomavirus Type 16 L1 protein	60μg
Recombinant Human Papillomavirus Type 18 L1 protein	40μg
Recombinant Human Papillomavirus Type 31 L1 protein	20μg
Recombinant Human Papillomavirus Type 33 L1 protein	20μg
Recombinant Human Papillomavirus Type 45 L1 protein	20μg
Recombinant Human Papillomavirus Type 52 L1 protein	20μg
Recombinant Human Papillomavirus Type 58 L1 protein	20μg

Excipients:
Aluminum hydroxide adjuvant, Sodium chloride, Sodium dihydrogen phosphate dihydrate, Disodium hydrogen phosphate dihydrate, Polysorbate 80 (II) and Water for injection.
There are no preservative or antibiotics in Cecolin 9 PFS.

3. PHARMACEUTICAL FORM:

Cecolin 9 PFS is presented as 0.5 mL suspension for injection in a pre-filled syringe.

Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

Cecolin 9 PFS would be a suspension after thorough agitation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cecolin 9 PFS is indicated for women aged 9-45 years[1,2].

At present, it has not been demonstrated that Cecolin 9 PFS has preventive effect on individual who had been infected by the vaccine types of HPV. The risk of exposure to HPV increases with age, especially after sexual debut. Therefore, it is recommended to vaccinate with Cecolin 9 PFS as early as possible.

Cecolin 9 PFS is indicated for the prevention of the following diseases caused by the HPV types contained in the vaccine (see section 5):

The following diseases caused by HPV types 16 and 18[3]:

- Cervical cancer
- Cervical intraepithelial neoplasia Grade 2 or 3 (CIN2/3) and adenocarcinoma in-situ (AIS)

  Cervical intraepithelial neoplasia Grade 1 (CIN1)

Clinical study data for persistent infection caused by HPV types 16, 18, 31, 33, 45, 52 and 58 have been obtained (see section 5 for details)[4]. The protective efficacy study on CIN, AIS and cervical cancer caused by HPV types 31, 33, 45, 52 and 58, as well as genital warts caused by HPV types 6 and 11, is ongoing[5].

[1] For age group 18-45 years, please refer to Section 13.4 Overall conclusion of the Phase III Clinical Study Report V1.0 in Module 5.3.5.
[2] For age group 9-17 years, please refer to Section 13.2 Overall Conclusions of the Immunogenicity Bridging Clinical Study Report V1.0 in Module 5.3.5.
[3] Please refer to Section 11.5.4.1 Efficacy for common types (HPV types 16 and 18) of the Phase III Clinical Study Report V1.0 in Module 5.3.5.
[4] Please refer to Section 11.5.4.2 Efficacy against non-common high-risk types (HPV types 31, 33, 45, 52, and 58) of the Phase III Clinical Study Report V1.0 in Module 5.3.5.
[5] Please refer to Section 9.2.2 Selection of Study Endpoints, Point 3) CIN2+ and/or VIN2+ and/or VaIN2+ lesion endpoint for the non-common high-risk types (HPV31/33/45/52/58) of the Phase III Clinical Study Report V1.0 in Module 5.3.5.

4.2 Posology and method of administration

Posology[6,7]

Age at the time of the first injection	Immunization and schedule
9 to and including 17 years	2 doses (0.5 mL/dose) at 0 and 6 months (with an interval of not less than 5 months) or 3 doses (0.5 mL/dose) at 0, 1 and 6 months*
From 18 years and above	3 doses (0.5 mL/dose) at 0, 1 and 6 months*

*According to the results of clinical studies of Cecolin 9 PFS (see section 5 for details), the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 4 months after the second dose. All three doses should be given within a 1year period.

At present, it has not been determined whether a booster vaccination is required for Cecolin 9 PFS.

Method of administration

1. Cecolin 9 PFS is injected intramuscularly and the preferred site for vaccination is deltoid muscle of upper arm. Intravascular or intradermal injection is prohibited. There has been no data on subcutaneous injection of Cecolin 9 PFS.
2. Cecolin 9 PFS should be shaken well before use and it is a white homogeneous suspension after shaking.
3. A separate sterile syringe and needle must be used for each vaccination.
4. Cecolin 9 PFS should be vaccinated as soon as possible after removal from the refrigeration container.

Any pre-filled syringe with crack, label unclear or invalid and vaccine with abnormal appearance should not be used.

4.3 Contraindications

1. Hypersensitivity to the active substances or to any of the excipients of the vaccine.
2. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Cecolin 9 PFS.

[6] For age group 9-17 years, please refer to Section 9.4.5 Immunization Route and Immunization Schedule of the Immunogenicity Bridging Clinical Study Report V1.0 in Module 5.3.5.
[7] For age group 18 years and above, please refer to Section 9.4.5 Immunization Schedule on Page 33 of the Phase III Clinical Study Report V1.0 in Module 5.3.5.

4.4 Special warnings and precautions for use

1. Vaccination cannot replace the routine cervical cancer screening or other measures to prevent HPV infection and sexually transmitted diseases. Therefore, routine cervical cancer screening remains extremely important as recommended by the relevant health administrative departments.

2. Prior to the vaccination of Cecolin 9 PFS, healthcare professionals should inquire and review the vaccinee's medical history (especially the previous vaccination history and any previous vaccination-related adverse reactions), and conduct clinical examination to evaluate the benefits and risks of vaccination. Cecolin 9 PFS is not recommended for populations other than those described in section 4.1.

3. As with other vaccines for injection, appropriate medical emergency measures and monitoring methods should be prepared to ensure that those who develop allergic reactions after the injection of Cecolin 9 PFS can be promptly treated.

4. Syncope: syncope (fainting) may occur after any dose of vaccine, leading to falls and injuries, especially in adolescents and young adults. Therefore, it is recommended that the observation on site be conducted for at least 30 minutes after each injection as required in the vaccination procedures.

It has been reported that syncope associated with tonic-clonic seizures and other epileptiform seizures may occur after the vaccination with similar products overseas. Syncope associated with tonic-clonic seizures is usually transient, and it can be resolved spontaneously when the vaccinee is placed in a supine or head-down position and the cerebral perfusion is restored. Some vaccinees may experience psychogenic reactions before/after the vaccination, and measures should be taken to avoid injury from the syncope.

5. As with other vaccines, the vaccination of Cecolin 9 PFS should be postponed in vaccinees suffering from acute severe febrile illness. In case of current or recent fever symptoms, whether to postpone the vaccination depends mainly on the severity of the symptoms and their etiology. Lowgrade fever and mild upper respiratory tract infection are not absolute contraindications to vaccination.

6. Cecolin 9 PFS should be used with caution in vaccinees with thrombocytopenia or any coagulation disorder.

7. As with any other vaccine, vaccination with Cecolin 9 PFS may not ensure the protective effect for all vaccinees.

8. Cecolin 9 PFS is only used for preventive purposes, but not indicated for the treatment of existing HPV-related lesions or preventing the progression of lesions.

9. Cecolin 9 PFS cannot prevent lesions caused by all high-risk types HPV infections. It has not been proved that Cecolin 9 PFS can prevent the lesions caused by the infection of non-vaccine types of HPV as well as the diseases not caused by HPV infection.

10. There are no data on the use of Cecolin 9 PFS in individuals with impaired immune system (such as patients receiving immunosuppressive agents). As with other vaccines, vaccination of Cecolin 9 PFS in immunocompromised individuals may not induce adequate immune response.

11. At present, the maximum protective period of Cecolin 9 PFS has not been fully established. In the Phase III clinical trial of Cecolin 9 PFS, the protective efficacy against persistent infection is followed up to 30 months (median: 32.0 months) after the first dose. See section 5.1 for specific results.

4.5 Interaction with other medicinal products and other forms of interaction

1. Since no clinical trial has been conducted for the vaccination of Cecolin 9 PFS combined with other vaccines, there is currently no relevant research data available.

2. The use of immunoglobulin or blood products should be avoided within 3 months prior to the vaccination of Cecolin 9 PFS.

3. There are no clinical evidence available to demonstrate whether the use of hormonal contraceptives will affect the preventive effect of Cecolin 9 PFS.

4. As with other vaccines, concomitant use of Cecolin 9 PFS with immunosuppressive agents may not induce an optimal active immune response in immunocompromised individuals.

5. At present, there are no clinical data available to support the interchangeable use among Cecolin 9 PFS and other HPV vaccines.

6. Due to the lack of incompatibility studies, the injection of Cecolin 9 PFS combined with other medicinal products is prohibited.

4.6 Pregnancy and lactation

Pregnancy

1. At present, there are no independent study conducted to systematically evaluate the effect of Cecolin 9 PFS on pregnant women. Data from clinical trials of Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Escherichia coli*) showed that no adverse effects on pregnancy outcomes and neonatal health status were observed in accidental vaccination during pregnancy or unexpected pregnancy events following vaccination. The limited data obtained from the clinical trials of Cecolin 9 PFS showed that pregnancy outcomes and neonatal health status were generally equivalent between the group receiving Cecolin 9 PFS and the group receiving Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Escherichia coli*) in accidental vaccination during pregnancy or unexpected pregnancy events following vaccination[8].
2. In animal studies, no direct or indirect adverse effects on reproduction, pregnancy, embryo/fetus development, parturition or postnatal development are observed after the vaccination of Cecolin 9 PFS.
3. Vaccination with Cecolin 9 PFS during pregnancy should be avoided. If a woman is pregnant or is determined to be pregnant, it is recommended to postpone or interrupt the vaccination schedule, and the rest of the vaccination schedule can complete after the end of pregnancy.

Lactating women

There are no clinical data on the use of Cecolin 9 PFS in lactating women. As many drugs can be secreted in breast milk, Cecolin 9 PFS should be used with caution in lactating women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

According to the classification of incidence of adverse reactions recommended by the Council for International Organizations of Medical Sciences (CIOMS), the adverse reactions are categorized by frequency using the following convention:

- Very common (≥10%),
- Common (1%-10%, including 1%),

[8] Please refer to Section 12.7 Summary of Safety Evaluation of the Phase III Clinical Study Report V1.0.

- Uncommon (0.1%-1%, including 0.1%),
- Rare (0.01%-0.1%, including 0.01%)
- Very rare (<0.01%).

The adverse reactions of Cecolin 9 PFS are described as follows:

A total of 4,851 female subjects aged 18-45 years[9] and 577 female subjects aged 9-17 years[10]

received at least one dose of Cecolin 9 PFS in three studies conducted in China: A Phase III trial evaluating protective efficacy of Cecolin 9 PFS, an immunogenicity bridging trial in individuals aged

9-17 years, and a comparative immunogenicity trial of Cecolin 9 PFS versus Recombinant Human Papillomavirus 9-Valent Vaccine (Gardasil 9).

Any immediate reactions should be observed and recorded in 30 minutes after each vaccination, and adverse reactions/events should be collected in 30 days after each dose. In addition, all serious adverse events during the observation period (30 months) should be recorded. The adverse reactions observed are listed as follow:

System Organ Class	**Frequency**	**Adverse reactions**
Systemic Adverse Reactions		
General disorders and administration site conditions	Common	Pyrexia, asthenia
Gastrointestinal disorders	Common	Nausea
	Uncommon	Diarrhoea, vomiting, abdominal pain
Nervous system disorders	Common	Headache, dizziness
Skin and subcutaneous tissue disorders	Uncommon	Pruritus
Immune system disorders	Uncommon	Hypersensitivity
	Common	Cough

[9] For female subjects aged 18-45 years, the total number 4851=4377+244+230:
1)Please refer to Table 1 Summary of Incidence of AEs in the Phase III Clinical Trial (Excluding the 575 Subjects) "4377 in the test group" of the Supplementary Information on the Clinical Trial Data.
2) Please refer to Section 12.1 Exposure Level "244 in the test group" of the Head-to-Head Clinical Study Report V1.0. 3)Please refer to Section 10.1 Subject Enrollment Status "230 18-26-year-old female subjects" of the Immunogenicity Bridging Clinical Study Report V1.0.

[10] Please refer to Section 10.1 Subject Enrollment Status "9-17-year-old subjects were randomized (577 females and 575 males)" on Page 49 of the Immunogenicity Bridging Clinical Study Report V1.0.

System Organ Class	Frequency	Adverse reactions
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinorrhoea, oropharyngeal pain, laryngeal pain, nasal obstruction, throat irritation
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Uncommon	Back pain
Local Adverse Reactions		
General disorders and administration site conditions	Very common	Vaccination site pain
	Common	Vaccination site pruritus, nodules, swelling, erythema, and discomfort

Tabulated list of post-marketing adverse events of similar products

In addition to the adverse reactions observed in the above clinical trials, the following adverse events have been spontaneously reported after the marketing of similar products worldwide. Due to these events were reported voluntarily from a population of uncertain size, it cannot be used to accurately evaluate the incidence rate or determine the relationship with the vaccination.

System Organ Class	Adverse events
General disorders and administration site conditions	Peripheral swelling
Cardiac disorders	Palpitations
Skin and subcutaneous tissue disorders	Allergic purpura
Vascular disorders	Pallor
Reproductive system and breast disorders	Vaginal discharge, vaginal haemorrhage, nipple pain
Nervous system disorders	Syncope or vasovagal reactions (sometimes associated with tonic-clonic seizures), acute disseminated encephalomyelitis, Guillain-Barre syndrome
Infections and infestations	Cellulitis
Blood and lymphatic system disorders	Primary immune thrombocytopenic purpura

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions is important for the evaluation of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to national regulatory authority for monitoring Adverse Events Following Immunisation (AEFI) or Adverse Drug Reactions. Where reporting to the national regulatory

authority is not possible, please log in the official website of Global Biotech Products Co., Ltd or send email to PV@gbp-th.com.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical studies

Five clinical studies of Cecolin 9 PFS have been completed in China (Table 1) to evaluate the protective efficacy and immunogenicity in females aged 9-45 years with 3-dose schedule (including pediatric population aged 9-17 years vaccinated with 2 doses).

Table 1. Summary of Main Clinical Studies of Cecolin 9 PFS Conducted in China (female subjects only)

Study No.	Phase	Study Design	Number of Subjects*			Study population
			Total	Cecolin 9 PFS Group	Control Group	
HPV-PRO-007[11]	Phase I	Single-center, doseescalation clinical trial	12	12	0	18-45 years
HPV-PRO-008[12]	Phase II	Randomized, doubleblind, adjuvant-controlled immunogenicity clinical trial	627	313	314	18-45 years
HPV-PRO-009[13]	Phase III	Randomized, doubleblind, Recombinant Human Papillomavirus Bivalent (Types 16,18) Vaccine (*Escherichia coli*)-controlled, multicenter clinical trial to evaluate protective efficacy (including immunogenicity)	8752	4377	4375	18-45 years

[11] Please refer to the Phase I Clinical Study Report V1.0.
[12] Please refer to the Phase II Clinical Study Report V1.0.
[13] Please refer to the Phase III Clinical Study Report V1.0 and Supplementary Information on the Clinical Trial Data.

HPV-PRO-011[14]	Phase III	Randomized, single-blind and Recombinant Human Papillomavirus 9-Valent Vaccine (Gardasil 9)controlled, immunogenicity comparative clinical trial	487	244	243	18-26 years
HPV-PRO-012[15]	Phase III	Randomized, controlled, immunobridging clinical trial	807	807	0	9-26 years

* Subjects who were enrolled and received at least one dose.

1. Protective Efficacy of Cecolin 9 PFS Against HPV Types 16 and 18

The HPV-PRO-009 study compared the immunogenicity (Table 2) of Cecolin 9 PFS and Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Escherichia. coli*) (hereinafter referred to as "HPV16/18 bivalent vaccine") as well as the incidence of persistent infection against HPV types 16 and 18. The results showed that in the per-protocol set (PPS) for immunogenicity, the seroconversion rates and geometric mean concentrations (GMCs) of neutralizing antibodies against HPV types 16 and 18 at 1 month after full-schedule vaccination (at Month 7) with Cecolin 9 PFS were non-inferior to those after vaccination with HPV16/18 bivalent vaccine. In subjects with negative results for corresponding HPV types at baseline (mITT, modified intention-to-treat), no persistent infection (≥12 months) in cervix caused by HPV types 16 and 18 was observed in the

Cecolin 9 PFS group and the HPV16/18 bivalent vaccine group at Month 30 (median time: 32.0 months). Based on comparison with the immunogenicity of HPV16/18 bivalent vaccine and intergroup comparison regarding the incidence of persistent infection, it can be inferred that Cecolin 9 PFS has good protective efficacy against HPV 16/18- related diseases and persistent infection.

[14] Please refer to the Head-to-Head Clinical Study Report V1.0.
[15] Please refer to the Immunogenicity Bridging Clinical Study Report V1.0.

Table 2. Neutralizing Antibody Responses* against HPV Types 16 and 18 Induced by Cecolin 9 PFS and the HPV16/18 Bivalent Vaccine in Females Aged 18–45 Years (At Month 7, PPS Population)**

Types	Cecolin 9 PFS			HPV16/18 Bivalent Vaccine		
	N	Seroconversion Rates % (95%CI)	GMC (95%CI)	N	Seroconversion Rates % (95%CI)	GMC (95%CI)
HPV 16	786	100.0 （99.5, 100.0）	440.8 （418.0, 464.9）	792	100.0 （99.5, 100.0）	729.3 （685.8, 775.4）
HPV 18	845	99.9 （99.3, 100.0）	183.2 （172.3, 194.7）	857	100.0 （99.6, 100.0）	286.7 （267.7, 307.1）

Note: N = Number of subjects included in analysis; 95%CI = 95% Confidence Interval; GMC = Geometric Mean Concentration.

* The neutralizing antibody test method was a pseudovirus-based neutralization assay (PBNA), and the international standard (IU/mL) from the National Institute for Biological Standards and Control (NIBSC) was used for quantification. Seroconversion rate: The proportion of subjects whose antibody level at 1 month after full-schedule vaccination (at Month 7) increased by 4 times or higher compared with that before vaccination.

** The PPS must meet the following criteria at the same time: having completed vaccination with all 3 doses after enrollment; no major protocol violation; negative for neutralizing antibodies against corresponding HPV types before vaccination (Day 0); negative HPV DNA test results for corresponding HPV types during the period from the day before vaccination to the day before the last dose (0 day-6 months); having completed valid serology tests at visits before vaccination and 1 month after full-schedule vaccination (at Month 7) .

2. Protective Efficacy of Cecolin 9 PFS Against HPV Types 6, 11, 31, 33, 45, 52, and 58[16]

In the HPV-PRO-009 study, a total of 9,327 female subjects aged 18-45 years were actually enrolled, and 8,752 subjects were included in efficacy analysis. The data on the number of persistent infection (≥12 months) as an endpoint event required for the study was collected at Month 30 after follow-up (median time: 32.0 months). Analysis of the primary endpoint (Table 3) was completed after review and confirmation by the Data Monitoring Committee (DMC). The results showed that in subjects with negative results for corresponding HPV types at baseline (mITT), the protective efficacy of Cecolin 9 PFS against two persistent infection (≥12 months) definitions related to newly targeted high-risk types (HPV types 31, 33, 45, 52, and 58) was 100.0% and 98.1%, respectively. By site, the protective efficacy of Cecolin 9 PFS against persistent infection (≥12 months) related to newly targeted high-risk types (HPV types 31, 33, 45, 52, and 58) in the cervix were 100.0%.

[16] Please refer to Table 4 (Page 8) and Table 5 (Page 10) in the Supplementary Information on the Clinical Trial Data

Table 3. Incidence of Persistent Infection (≥12 Months) with Newly Targeted High-Risk HPV Types (HPV 31, 33, 45, 52, and 58) in Females Aged 18-45 Years (mITT Population*)

Study Endpoint	Cecolin 9 PFS		HPV 16/18 Bivalent Vaccine		Protective Efficacy % (95% CI)
	N	Number of Cases	N	Number of Cases	
Definition 1**	2571	0	2526	28	100.0 (86.3, 100.0)
Cervix	2559	0	2512	10	100.0 (56.5, 100.0)
Non-cervical site	2571	0	2526	26	100.0 (85.2, 100.0)
Definition 2***	3897	1	3904	53	98.1 (89.2, 100.0)
Cervix	3895	0	3899	26	100.0 (84.9, 100.0)
Non-cervical site	3897	1	3903	49	98.0 (88.2, 100.0)

Note: N = Number of subjects included in analysis; 95% CI = 95% confidence interval.

* The mITT must meet the following criteria at the same time: having completed vaccination with at least one dose after enrollment; negative for neutralizing antibodies against corresponding HPV types before vaccination (Day 0); negative HPV DNA test results for corresponding HPV types from Day 0 to Month 6, completed gynecological visits after Month 6 sufficient for endpoint assessment, and efficacy evaluation began post-Month 6.

In efficacy analysis regarding definition 1, 2 subjects in the Cecolin 9 PFS group (2,571 subjects) and 1 subject in the HPV16/18 bivalent vaccine group (2,526 subjects) did not complete full-schedule vaccination. In efficacy analysis regarding definition 2, 5 subjects in the Cecolin 9 PFS group (3,897 subjects) and 5 subjects in the HPV16/18 bivalent vaccine group (3,904 subjects) did not complete full-schedule vaccination. None of the subjects who did not complete full-schedule vaccination in the two groups experienced persistent infection (≥12 months) with newly targeted high-risk types.

** Definition 1: Presence of at least three consecutive HPV DNA-positive results (an interval of 150-210 days between every two results) for specimens from the same site and of the same HPV type at an interval of about 12 months (≥300 days), and the absence of a negative DNA sample among the three positive DNA samples.

*** Definition 2: Presence of at least two consecutive HPV DNA-positive results for specimens from the same site and of the same HPV type at an interval of about 12 months (≥300 days), and the absence of a negative DNA sample between the two positive DNA samples.

The protective efficacy study on CIN, AIS and cervical cancer caused by HPV types 31, 33, 45, 52 and 58, as well as genital warts caused by HPV types 6 and 11, is ongoing.

3. Immunogenicity

(1) Results of comparison with the immunogenicity of the similar product[17]

[17] Please to the Table 11.6.2 and Table 11.6.3 in the Head-to-Head Clinical Study Report V1.0.

In the HPV-PRO-011 study, the immunogenicity of Cecolin 9 PFS and marketed Recombinant Human Papillomavirus 9-Valent Vaccine (Gardasil 9) was evaluated (Table 4). The results showed that in the per-protocol set (PPS) for immunogenicity, the seroconversion rates and GMCs of neutralizing antibodies against all HPV types at 1 month after full-schedule vaccination (at Month 7) with Cecolin 9 PFS were non-inferior to those after vaccination with Gardasil 9.

Table 4. Results of Immunogenicity Comparison Between Cecolin 9 PFS and Gardasil 9* (At Month 7, PPS Population)**

Types	Cecolin 9 PFS			Recombinant Human Papillomavirus 9-Valent Vaccine (Gardasil 9)		
	N	Seroconversion Rates % (95%CI)	GMC (95% CI)	N	Seroconversion Rates % (95%CI)	GMC (95% CI)
HPV 6	209	100.0 (98.3, 100.0)	468.5 (411.5, 533.4)	220	100.0 (98.3, 100.0)	447.2 (394.1, 507.4)
HPV 11	222	100.0 (98.4, 100.0)	273.0 (240.9, 309.4)	223	100.0 (98.4, 100.0)	343.4 (309.5, 381.0)
HPV 16	218	100.0 (98.3, 100.0)	788.5 (694.3, 895.5)	217	100.0 (98.3, 100.0)	819.5 (721.5, 930.7)
HPV 18	222	100.0 (98.4, 100.0)	276.8 (244.4, 313.3)	223	100.0 (98.4, 100.0)	341.0 (301.8, 385.3)
HPV 31	219	100.0 (98.3, 100.0)	1001.7 (874.7, 1147.1)	219	100.0 (98.3, 100.0)	977.2 (862.2, 1107.6)
HPV 33	219	100.0 (98.3, 100.0)	508.2 (446.7, 578.1)	218	100.0 (98.3, 100.0)	518.2 (457.9, 586.4)
HPV 45	220	100.0 (98.3, 100.0)	182.4 (160.2, 207.7)	222	100.0 (98.4, 100.0)	170.9 (148.1, 197.1)
HPV 52	222	100.0 (98.4, 100.0)	399.9 (359.2, 445.2)	222	100.0 (98.4, 100.0)	367.8 (332.0, 407.4)
HPV 58	206	100.0 (98.2, 100.0)	857.7 (753.1, 976.8)	212	100.0 (98.3, 100.0)	519.3 (460.6, 585.5)

Note: N = Number of subjects included in analysis; 95%CI = 95% Confidence Interval; GMC = Geometric Mean Concentration.

* The neutralizing antibody test method was a pseudovirus-based neutralization assay (PBNA), and each type was quantified with the corresponding international standard (IU/mL) (HPV types 16 and 18), China national standard (U/mL) (HPV types 6, 33, 45, 52, and 58), and in-house reference standard (YU/mL) (HPV types 11 and 31). Seroconversion rate: The proportion of subjects whose antibody level at 1 month after full-schedule vaccination (at Month 7) increased by 4 times or more compared with that before vaccination.

** The PPS must meet the following criteria at the same time: having completed vaccination with all 3 doses after enrollment; no major protocol violation; negative for neutralizing antibodies against corresponding HPV

types before vaccination (Day 0); having completed valid serology tests at visits before vaccination and 1 month after full-schedule vaccination (at Month 7).

(2) Immunogenicity Results from the Bridging Study in Females Aged 9-17 Years[18]

The HPV-PRO-012 study assessed the immunogenicity of Cecolin 9 PFS in females aged 9-17 years with 2-dose schedule, and in females aged 9-17 years with 3-dose schedule, and in females aged 18-26 years with 3-dose schedule (Table 5). In the per-protocol set (PPS) for immunogenicity, the results demonstrated that at 1 month after full-schedule vaccination (at Month 7) the neutralizing antibodies in females aged 9-17 years with both the 2-dose and 3-dose schedules were non-inferior to those in females aged 18-26 years with 3-dose schedule.

The study on the immune persistence in the females aged 9-17 years vaccinated with Cecolin 9 PFS is ongoing.

Table 5. Immunogenicity Results* from the Bridging Study in Females Aged 9–17 Years (At Month 7, PPS Population)**

Types	N	Seroconversion Rates % (95%CI)	Rate Difference % (95% CI)	GMC (95% CI)
HPV 6				
Females Aged 18-26 Years (3-dose group)	192	100.0 (98.1, 100.0)	-	246.6 (216.2, 281.4)
Females Aged 9-17 Years (2-dose group)	267	100.0 (98.6, 100.0)	0.0 (-1.4, 2.0)	224.0 (202. 8, 247.5)
Females Aged 9-17 Years (3-dose group)	267	100.0 (98.6, 100.0)	0.0 (-1.4, 2.0)	331.5 (294.3, 373.4)
HPV 11				
Females Aged 18-26 Years (3-dose group)	196	98.5 (95.6, 99.7)	-	150.1 (131.5, 171.3)
Females Aged 9-17 Years (2-dose group)	269	98.9 (96.8, 99.8)	0.4 (-1.7, 2.5)	131.8 (119.7, 145.0)
Females Aged 9-17 Years (3-dose group)	269	98.9 (96.8, 99.8)	0.4 (-1.7, 2.5)	254.5 (225.3, 287.5)
HPV 16				
Females Aged 18-26 Years (3-dose group)	191	100.0 (98.1, 100.0)	-	382.4 (328.2, 445.5)

[18] Please refer to the Table 11.6.3 and Table 11.6.4 in the Immunogenicity Bridging Clinical Study Report V1.0.

Females Aged 9-17 Years (2-dose group)	268	100.0 (98.6, 100.0)	0.0 (-1.4, 2.0)	561.6 (501.4, 629.0)
Females Aged 9-17 Years (3-dose group)	269	100.0 (98.6, 100.0)	0.0 (-1.4, 2.0)	712.8 (627.3, 810.1)
HPV 18				
Females Aged 18-26 Years (3-dose group)	195	99.0 (96.3, 99.9)	-	111.1 (96.8, 127.6)
Females Aged 9-17 Years (2-dose group)	270	98.5 (96.3, 99.6)	-0.5 (-2.5, 1.6)	115.2 (102.5, 129.4)
Females Aged 9-17 Years (3-dose group)	270	99.3 (97.3, 99.9)	0.3 (-1.5, 2.0)	205.5 (178.6, 236.5)
HPV 31				
Females Aged 18-26 Years (3-dose group)	194	100.0 (98.1, 100.0)	-	478.0 (418.6, 545.7)
Females Aged 9-17 Years (2-dose group)	268	100.0 (98.6, 100.0)	0.0 (-1.4, 1.9)	464.8 (423.9, 509.7)
Females Aged 9-17 Years (3-dose group)	270	100.0 (98.6, 100.0)	0.0 (-1.4, 1.9)	903.8 (796.7, 1025.4)
HPV 33				
Females Aged 18-26 Years (3-dose group)	194	100.0 (98.1, 100.0)	-	275.9 (241.3, 315.5)
Females Aged 9-17 Years (2-dose group)	269	100.0 (98.6, 100.0)	0.0 (-1.4, 1.9)	344.5 (308.6, 384.6)
Females Aged 9-17 Years (3-dose group)	269	100.0 (98.6, 100.0)	0.0 (-1.4, 1.9)	471.1 (415.4, 534.2)
HPV 45				
Females Aged 18-26 Years (3-dose group)	196	99.5 (97.2, 100.0)	-	97.7 (85.0, 112.3)
Females Aged 9-17 Years (2-dose group)	269	99.6 (97.9, 100.0)	0.1 (-1.1, 1.4)	79.4 (72.4, 87.1)
Females Aged 9-17 Years (3-dose group)	270	99.6 (98.0, 100.0)	0.1 (-1.1, 1.4)	176.7 (154.2, 202.5)
HPV 52				
Females Aged 18-26 Years (3-dose group)	195	100.0 (98.1, 100.0)	-	252.5 (224.6, 283.8)
Females Aged 9-17 Years (2-dose group)	270	99.3 (97.3, 99.9)	-0.7 (-1.8, 0.3)	231.3 (212.9, 251.3)

Females Aged 9-17 Years (3-dose group)	270	99.6 (98.0, 100.0)	-0.4 (-1.1, 0.4)	416.8 (373.7, 464.8)
HPV 58				
Females Aged 18-26 Years (3-dose group)	194	100.0 (98.1, 100.0)	-	346.9 (304.6, 395.0)
Females Aged 9-17 Years (2-dose group)	269	100.0 (98.6, 100.0)	0.0 (-1.4, 1.9)	430.5 (387.6, 478.1)
Females Aged 9-17 Years (3-dose group)	267	100.0 (98.6, 100.0)	0.0 (-1.4, 1.9)	523.4 (465.8, 588.0)

Note: N = Number of subjects included in analysis; 95%CI = 95% Confidence Interval; GMC = Geometric Mean Concentration; each difference in seroconversion rate was obtained based on comparison with females aged 1826 years (3-dose group).

* The neutralizing antibody test method was a pseudovirus-based neutralization assay (PBNA), and each type was quantified with the corresponding international standard (IU/mL) (HPV types 16 and 18), China national standard (U/mL) (HPV types 6, 33, 45, 52, and 58), and in-house reference standard (YU/mL) (HPV types 11 and 31). Seroconversion rate: The proportion of subjects whose antibody level at 1 month after full-schedule vaccination (at Month 7) increased by 4 times or higher compared with that before vaccination.

** The PPS must meet the following criteria at the same time: having completed vaccination with all doses after enrollment; no major protocol violation; negative for neutralizing antibodies against corresponding HPV types before vaccination (Day 0); having completed valid serology tests at visits before vaccination and 1 month after full-schedule vaccination (at Month 7).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients See

section 2.

6.2 Incompatibilities

In the absence of compatibility studies, Cecolin 9 PFS must not be mixed with other

medicinal products.

6.3 Shelf life 24 months.

6.4 Special precautions for storage

Cecolin 9 PFS must be stored at 2°C to 8°C (36ºF and 46ºF) and protected from light. DO NOT FREEZE. Discard if vaccine has been frozen.

6.5 Nature and contents of container

Cecolin 9 PFS is supplied as a carton of one single-dose pre-filled syringe (size: 1 mL, borosilicate glass, with a halogenated butyl rubber plunger).

6.6 Special precautions for disposal and other handling

Cecolin 9 PFS should be shaken well before use, and it should be a white homogeneous suspension after shaking.

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Manufacturer Xiamen Innovax Biotech Co., Ltd. Address of Manufacturing Site: No. 52 and No. 60, Shanbianhong East Road, Haicang District, Xiamen City, Fujian Province, China

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