Supplementary appendix

Safety and immunogenicity of a bivalent HPV16/18 vaccine in Chinese females

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Supplementary Table 1. Local Reaction Grading

Local reaction	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)	Potentially life-threatening (grade 4)
Pain	Without affecting activities	Affecting activities or using non-narcotic analgesics many times	Affecting daily activities or using narcotic analgesics many times	Requiring emergency treatment or hospitalization
Induration *	<15 mm	15~30 mm	>30 mm	Gangrene or exfoliative dermatitis
Redness *	<15 mm	15~30 mm	>30 mm	Gangrene or exfoliative dermatitis
Swelling **	<15 mm without affecting activities	15 - 30 mm or affecting activities	> 30 mm or limiting daily activities	Gangrene
Rash (injection site)	<15 mm	15~30 mm	>30 mm	/
Itching	Slightly itchy in injection site	Moderately itchy in injection limb	Itchy all over	/

Guidelines for Adverse Reaction Classification Standards for Clinical Trials of Preventive Vaccines. 2005
Available from: https://www.nmpa.gov.cn/xxgk/fgwj/gzwj/gzwjyp/20051014010101369_5.html

Supplementary Table 2. Systemic reactions grading

Systemic reactions / Vital signs	Mild (grade 1)	Moderate (grade 2)	Serious (grade 3)	Potentially life-threatening (grade 4)
Fever (axillary temperature)	37.1–37.5°C	37.6–39.0°C	> 39.0°C	
Allergic reaction	Itching without rash	Local urticaria	Extensive urticaria, angioedema	Severe allergic reaction
Headache	Without affecting activities requiring treatment	Transient, slightly affecting activities, requiring treatment (multiple use of non-narcotic analgesics)	Seriously affecting daily activities, with initial anesthetic treatment response	Refractory, requiring repeated anesthetic treatment. Requiring emergency treatment or hospitalization
Fatigue, tiredness	Normal activities weakened for < 48 hours, without affecting activities	20–50% of normal activities weakened for > 48 hours, slightly affecting activities	More than 50% of normal activities weakened, seriously affecting daily activities, and causing out of work	Incapable of taking care of themselves, requiring emergency treatment or hospitalization
Nausea, vomiting	1–2 times / 24 hours, basically normal intake, without affecting activities	2–5 times / 24 hours, significantly decreased intake, or limited activities	> 6 times within 24 hours, no obvious intake, requiring intravenous infusion	Requiring hospitalization or other nutrition due to hypotensive shock
Diarrhea	Mild or transient, 2 - 3 loose stools / day, or mild diarrhea lasting for less than 1 week	Moderate or persistent, 4–5 times / day, or diarrhea > 1 week	> 6 watery stools/day, or bloody diarrhea, orthostatic hypotension, electrolyte imbalance, requiring intravenous infusion > 2 L	Hypotensive shock, requiring hospitalization
Myalgia	Without affecting daily activities	Muscle tenderness at non-injection site, slightly affecting daily activities	Severe muscle tenderness, seriously affecting daily activities	Obvious symptoms, muscle necrosis, requiring emergency treatment or hospitalization
Other discomfort or clinical adverse reactions	Without affecting activities	Slightly affecting activities, requiring no medication	Seriously affecting daily activities, requiring medication	

Supplementary Table 3. Causality assessment criteria

- Definitely unrelated: AEs occurred due to other factors, such as clinical condition of the subject, other treatments, or concomitant medication.
- Possibly unrelated: AEs occurred possibly due to other factors, such as clinical condition of subjects, other treatments, or concomitant medications, which were inconsistent with the known information of study vaccine.
- Possibly related: AEs were consistent with the known information of study vaccine and had a causal relationship with the study vaccine, but might also be related to other factors.
- Probably related: AEs were consistent with the known information of study vaccine, and had a causal relationship with study vaccine, which could not be explained by other factors, such as clinical condition of the subject, other treatments, or concomitant medication.
- Certainly related: AEs were consistent with the known information of study vaccine, and had a causal relationship with study vaccine, which could not be explained by other factors, such as clinical condition of the subject, other treatments, or concomitant medication. In addition, when the study vaccine was used again, AEs would occur repeatedly.

Supplementary table 4. Demographic characteristics of the participants included in the Safety Set [a]

Characteristic	All participants	
	Placebo	**Vaccine**
N =	600	597
Age (y), median	17.8	18.0
Height (cm), median	153	153
Weight (kg), median	46.0	46.5
Ethnic group (n)		
Han	489	496
Zhuang	47	37
Yao	63	59
Other	1	5

Supplementary table 5. Baseline seropositivity rates of the participants included in the Safety Set [a]

	HPV16			HPV18		
	Placebo	**Vaccine**	***p***	**Placebo**	**Vaccine**	***p***
Baseline seropositivity rates (n, %)						
All	11 (1.8)	21 (3.5)	***0.071****	16 (2.7)	22 (3.7)	*0.315*
9–17 years	1 (0.3)	3 (1.0)	*0.624*	6 (2.0)	5 (1.7)	*1.000*
18–26 years	5 (4.2)	4 (3.3)	*1.000*	4 (3.3)	5 (4.2)	*1.000*
27–45 years	5 (2.8)	14 (7.9)	***0.031****	6 (3.3)	12 (6.8)	*0.137*
Baseline neutralising GMTs[b]						
All	20.6	21.2	*0.137*	20.8	21.1	*0.295*
9–17 years	20.1	20.5	*0.225*	20.6	20.7	*0.738*
18–26 years	21.2	21.4	*0.828*	21.0	21.1	*0.875*
27–45 years	21.1	22.2	*0.229*	21.0	21.9	*0.235*

* indicates significant differences were observed between groups.
a. Safety Set included enrolled participants who received at least one dose of vaccine or placebo.
b. GMTs indicates geometric mean neutralisation titres.

Supplementary table 6. Month 7 neutralising antibody responses as geometric mean titres (GMTs) and seroconversion rates (SCR) in initially seropositive participants

Antibody	Population	Placebo group				Vaccine group			
		N	Seroconverted n (%)	GMT (95%CI),		N	Seroconverted n (%)	GMT (95%CI),	
				Month 7					
HPV16	All participants	8	1 (12.5)	95.1	(48.4, 187)	20	20 (100)	7241	(4604, 11386)
	9–17 years	1	0	20.0	(-, -)	3	3 (100)	25803	(716, 929700)
	18–26 years	3	0	80.0	(14.3, 448)	3	3 (100)	5120	(915, 28646)
	27–45 years	4	1 (25.0)	160	(160, 160)	14	14 (100)	5940	(3901, 9046)
HPV18	All participants	14	0	24.4	(17.5, 33.9)	20	20 (100)	4017	(2095, 7704)
	9–17 years	5	0	20.0	(20.0, 20.0)	5	5 (100)	11763	(1820, 76004)
	18–26 years	3	0	20.0	(20.0, 20.0)	4	4 (100)	5120	(2080, 12600)
	27–45 years	6	0	31.8	(13.2, 76.6)	11	11 (100)	2557	(937, 5436)

Supplementary table 7. Participants reporting adverse events, serious adverse events and solicited local reactions and systemic adverse events after any dose of vaccine or placebo in the Safety Set[a]

	All participants		9–17 years cohort		18–26 years cohort		27–45 years cohort	
	Placebo	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**	**Vaccine**
N =	600	599	300	300	120	120	180	179
Any adverse event, n (%) [b]								
Any	435 (72.5)	418 (69.8)	241 (80.3)	227 (75.7)	94 (78.3)	91 (75.8)	100 (55.6)	100 (55.9)
Grade 3	**17 (2.8)**	**19 (3.2)**	**10 (3.3)**	**12 (4.0)**	**5 (4.2)**	**3 (2.5)**	**2 (1.1)**	**4 (2.2)**
Dose 1	323 (53.8)	289 (48.3)	183 (61.0)	165 (55.0)	72 (60.0)	59 (49.2)	68 (37.8)	65 (36.3)
Grade 3	**3 (0.5)**	**8 (1.3)**	**1 (0.3)**	**5 (1.7)**	**2 (1.7)**	**2 (1.7)**	**0**	**1 (0.6)**
Dose 2	248 (43.0)	239 (41.3)	152 (51.7)	135 (46.6)	47 (42.3)	58 (51.8)	49 (28.5)	46 (26.0)
Grade 3	**10 (1.7)**	**5 (0.9)**	**8 (2.7)**	**2 (0.7)**	**1 (0.9)**	**1 (0.9)**	**1 (0.6)**	**2 (1.1)**
Dose 3	162 (28.9)	168 (30.0)	95 (33.0)	112 (39.2)	36 (35.0)	33 (31.7)	31 (18.2)	23 (13.5)
Grade 3	**1 (0.2)**	**5 (0.9)**	**0**	**5 (1.8)**	**0**	**0**	**1 (0.6)**	**0**

a. Safety Set includes all participants who received at least one dose of vaccine or placebo.

b. Includes solicited local reactions and systemic adverse events and unsolicited adverse events.

Supplementary table 8. Details of withdrawals because of any adverse event

Vaccine group					Placebo group				
	Reasons for withdrawal					Reasons for withdrawal			
Case no.	**Age (yrs)**	**Type of event**	**Dose**	**Time post vaccination (day)**	**Case no.**	**Age (yrs)**	**Type of event**	**Dose**	**Time post vaccination (day)**
1	45.4	Uterine cervix hyperplasia	1	56	1	15.3	Pyrexia	1	6
					2	35.7	Heavy menstrual bleeding	1	24

From study start up to Month 12, in total, 3 subjects prematurely discontinued the study due to an AE/SAE:
Participant #1 in the vaccine group prematurely discontinued the study due to the SAE of cervical intraepithelial neoplasia III (CIN III). The participant was hospitalized for pan hysterectomy 56 days after the first dose of vaccine. This SAE was considered by the investigator as not related to study vaccine.
Participant #1 in the Placebo group prematurely discontinued the study due to an AE of pyrexia (38.8℃) that started 6 days after the first dose.
Participant #2 in the Placebo group prematurely discontinued the study due to an AE of heavy menstrual bleeding started 24 days after the first dose.

Supplementary table 9. Overall pregnancy outcomes

	Placebo group	Vaccine group
Pregnancies (events reported, n)	9	15
Live birth		
- Normal delivery (n, %)	5 (56)	8 (53)
Abortion		
- Elective abortion (n, %)	3 (33)	7 (47)
- Spontaneous abortion (n, %)	1*(11)	0

n: Number of subjects report at least one specified event;

* One case of spontaneous abortion occurred in the placebo group due to premature rupture of membranes.