The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 112949 (HPV-063 EXT 032)

Title: Long-term extension study of the efficacy of the 580299 vaccine in the prevention of HPV-16 and/or HPV-18 associated cervical intraepithelial neoplasia (CIN) in Japanese women vaccinated in the primary vaccination study HPV-032. *Cervarix*™ - 580299 (HPV): GlaxoSmithKline (GSK) Biologicals' virus-like particle (VLP) vaccine against human papillomaviruses (HPVs) 16/18.

Rationale: This study was conducted to assess the HPV vaccine efficacy against CIN lesions, cervical cancer and cytological abnormalities associated with HPV-16 and/or HPV-18 or other oncogenic HPV types for up to 48 months after administration of the first dose of vaccine in 104798 (HPV-032) primary vaccination study. Vaccine efficacy against incident and persistent infection was also assessed. In addition, safety and persistence of the humoral immune response were evaluated in this study.
The control Group had received Aimmugen™ vaccine in the primary study.
Aimmugen™: Kaketsuken's freeze-dried inactivated tissue culture Hepatitis A vaccine (HAV).
Results from the primary vaccination are presented in 104798 (HPV-032) CTRS.

Phase: II

Study Period: From 20 June 2009 to 21 February 2011

Study Design: An open, randomized* (1:1), multi-centre, controlled study with 2 parallel groups.
*Randomisation occurred in primary vaccination study 104798.

Centres: 13 centres in Japan

Indication: Active immunization of girls and women from 9 years of age onwards for the prevention of persistent HPV infections premalignant cervical lesions and cervical cancer (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV).

Treatment: No vaccine was administered in this study.
The study groups were as follows:

- HPV Group: subjects received 3 doses of HPV vaccine in primary vaccination study 104798.
- HAV Group: subjects received 3 doses of HAV vaccine in primary vaccination study 104798.

Objectives:

- To estimate the efficacy of the HPV-16/18 L1 VLP AS04 vaccine in the prevention of histopathologically-confirmed CIN1+ (CIN1, CIN2, CIN3, Adenocarcinoma in situ [AIS], Invasive Cervical Cancer [ICC]) associated with HPV-16 and/or HPV-18 in the HPV-063 study in Japanese healthy adult women (vaccinated at 20-25 years of age), who were, for the corresponding HPV type, seronegative at Month 0 (by ELISA) and HPV Deoxyribonucleic acid (DNA) negative (by polymerase chain reaction [PCR]) at Months 0 and 6 in the primary vaccination study HPV-032.

Primary Outcome/Efficacy Variable:

- Histopathologically confirmed low-grade cervical lesions and higher lesions concurrently associated with oncogenic HPV types targeted by the vaccine.
  - Low-grade cervical lesions and higher lesions are defined as CIN 1+, i.e. CIN1, CIN2, CIN3, AIS and ICC.
  - Based on detection of vaccine oncogenic HPV types (HPV-16 or HPV-18) within the lesional component of the cervical tissue specimen (by PCR) at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, seronegative at Month 0 (by ELISA) and HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032].

Secondary Outcome/Efficacy Variable(s):

- Histopathologically confirmed low-grade cervical lesions and higher lesions concurrently associated with oncogenic HPV types targeted by the vaccine.
  - Low-grade cervical lesions and higher lesions are defined as CIN1+, i.e. CIN1, CIN2, CIN3, AIS and ICC.
  - Based on detection of vaccine oncogenic HPV types (HPV-16 or HPV-18) within the lesional component of the cervical tissue specimen (by PCR) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, seronegative (by ELISA) at Month 0 and HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary HPV-032 study].
- Cytologically confirmed abnormalities and lesions concurrently associated with oncogenic HPV types targeted by the vaccine.
  - Cytologically confirmed abnormalities and lesions are defined as atypical squamous cell of undetermined significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous

intraepithelial lesions (HSIL).
  - Based on detection of vaccine oncogenic HPV types (HPV-16 or HPV-18) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, seronegative (by ELISA) at Month 0 and HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032].
- Cytologically confirmed abnormalities and lesions concurrently associated with oncogenic HPV types.
  - Cytologically confirmed abnormalities and lesions are defined as ASC-US, LSIL, HSIL.
  - Based on detection of oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 or 68) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032].
- Histopathologically confirmed low-grade cervical lesions and higher lesions concurrently associated with oncogenic HPV types.
  - Low-grade cervical lesions and higher lesions are defined as CIN1+, i.e. CIN1, CIN2, CIN3, AIS and ICC.
  - Based on detection of oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 or 68) within the lesional component of the cervical tissue specimen (by PCR) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032]
- Incident cervical infection associated with oncogenic HPV types targeted by the vaccine.
  - Based on the detection of HPV-16 and/or HPV-18 (by PCR) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, seronegative (by ELISA) at Month 0 and HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032].
- Incident cervical infection associated with oncogenic HPV types.
  - Based on the detection of oncogenic HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68; by PCR) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032].
- Persistent long-term cervical infection with oncogenic HPV types targeted by the vaccine.
  - Long-term persistent infection (using the 12-month definition*) associated with HPV-16 and/or HPV-18 (by PCR) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, seronegative at Month 0 (by ELISA) and HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032].
- Persistent long-term cervical infection with oncogenic HPV types.
  - Long-term persistent infection (using the 12-month definition) associated with any oncogenic HPV type (including HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68; by PCR) at HPV-032 or at HPV-063 study visits [as assessed in women who were, for the corresponding HPV type, HPV DNA negative (by PCR) at Month 0 and Month 6 in the primary vaccination study HPV-032].
- Immunogenicity with respect to components of the investigational vaccine.
  - HPV-16 and HPV-18 seropositivity rates, and geometric mean titres (GMTs) assessed by ELISA in the HPV Group at Month 0 [Month 36 EXT 032] and at Month 12 [Month 48 EXT 032].
- Occurrence of Serious Adverse Events (SAEs) from last HPV-032 study visit (Month 24) until end of the HPV-063 study (Month 12 [Month 48 EXT 032]) and from Month 0 in the HPV-032 study until HPV-063 study end.
- Occurrence of New Onset of Chronic Diseases (NOCDs) (including New Onset of Autoimmune Diseases (NOADs)) from last HPV-032 study visit (Month 24) until end of the HPV-063 study (Month 12 [Month 48 EXT 032]) and from Month 0 in the HPV-032 study until HPV-063 study end, regardless of causal relationship to vaccination and intensity.
- Occurrence of medically significant conditions (MSCs), defined as Adverse Events (AEs) prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases from last HPV-032 study visit (Month 24) until end of the HPV-063 study (Month 12 [Month 48 EXT 032]) and from Month 0 in the HPV-032 study until HPV-063 study end.
- Pregnancies and pregnancy outcomes from last HPV-032 study visit (Month 24) until end of the HPV-063 study (Month 12 [Month 48 EXT 032]) or until delivery when delivery occurs after HPV-063 study end and from Month 0 in the HPV-032 study until HPV-063 study end (or until delivery when delivery occurs after HPV-063 study end).

* Persistent infection (12-month definition): Detection of at least 2 positive HPV DNA PCR assays for the same viral genotype with no negative DNA sample between the 2 positive DNA samples, over an approximate interval of 12 months (> 300 days).

Statistical Methods: The analyses were performed on the Total Vaccinated cohort (pooled), Total Vaccinated cohort M48 EXT-032, According-to-protocol (ATP) cohort for immunogenicity M48 EXT-032, ATP cohort for efficacy M48 EXT-032 and on ATP cohort for efficacy (pooled).

- The Total Vaccinated cohort (pooled) included all vaccinated subjects in the primary study 104798 and for whom data were available in the primary study 104798 or in the current follow-up study
- Total Vaccinated cohort M48 EXT-032 included all subjects from Total Vaccinated cohort who came for the current follow-up study.
- ATP cohort for immunogenicity M48 EXT-032 included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria) for whom data concerning immunogenicity outcome measures were available in this current follow-up study for antibodies against at least one study vaccine antigen component.
- ATP cohort for efficacy M48 EXT-032 included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination violations), who received 3 doses of study vaccine, who had a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0 in the primary vaccination, who should be negative for HPV DNA (by PCR) at Month 0 and Month 6 in the primary vaccination study for the HPV-type considered in the analysis, for whom data concerning efficacy outcome measures were available in this current follow-up study.
- The ATP cohort for efficacy (pooled) included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination violations) who received 3 doses of study vaccine, who had a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0 in the primary vaccination, who should be negative for HPV DNA (by PCR) at Month 0 and Month 6 in the primary vaccination study for the HPV-type considered in the analysis, for whom data concerning efficacy outcome measures, in the primary study 104798 or in the current follow-up study.

Analysis of efficacy

The analysis was performed on the ATP cohort for efficacy M48 EXT-032 with 12-month follow-up during study HPV-063 and on the ATP cohort for efficacy (pooled) with 48-month follow-up during the entire period of studies HPV-032 and HPV-063 combined.

For all histopathological endpoints, the cases were defined using the HPV type assignment algorithm (HPV TAA), i.e., the association between the lesion and the HPV type was not only based on the detection of HPV DNA in the lesion, but also on the presence of HPV type(s) in one of the 2 immediately preceding cytology samples in case more than one HPV type was found in the lesion.

The estimation of vaccine efficacy was performed per treatment actually administered in the primary vaccination study HPV-032.

The vaccine efficacy (VE) for all outcome variables was tabulated with 95% confidence interval (CI) using a conditional exact method that took into account the follow-up time of the subjects within each group and p-values were calculated using the Fisher's exact test.

Vaccine efficacy was calculated as follows:

$VE=1-[(n_1/T_1) / (n_2/T_2)]$

where

n_1= number of subjects reporting at least one event in the HPV Group,

n_2= number of subjects reporting at least one event in the HAV Group,

T_1 (years) = sum of follow-up period (censored at the first occurrence of an event) expressed in years in HPV Group

T_2 (years) = sum of follow-up period (censored at the first occurrence of an event) expressed in years in HAV Group

VE(%) = vaccine efficacy.

No sample size was calculated for this HPV-032 extension study and the analysis of efficacy was only descriptive using a 95% CI around the vaccine efficacy estimate calculated using the conditional exact method.

Analysis of Immunogenicity

The analysis was performed on the ATP cohort for immunogenicity M48 EXT-032.

Seropositivity rates and GMTs for HPV-16 and HPV-18 antibodies were tabulated with 95% CI at each time point for which a serological result was available for HPV Group.

Analysis of Safety

The analysis was performed on the Total Vaccinated cohort (pooled) wherein the data were collected during the entire follow-up period of studies HPV-032 and HPV-063 combined and on the Total Vaccinated cohort M48 EXT-032 wherein the data were collected during the follow-up period from last visit in study HPV-032 (Month 24) until the last visit in study HPV-063.

The percentages of subjects with SAEs, NOCDs (including NOADs) and MSCs reported during the Month 24 - Month 48 and Month 0 - Month 48 follow-up periods were tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) for each group.
Pregnancies and pregnancy outcomes reported in the follow-up periods, Month 24 - Month 48 and Month 0 - Month 48, were tabulated for each group.

Study Population: Healthy Japanese women aged 20 to 25 years at the time of first vaccination who had received at least 1 dose of study vaccine in study HPV-032 and who were not diagnosed with high grade or missing cytology at Month 0 in the HPV-032 study were enrolled in the study. Pregnant females and females who were pregnant less than 3 months ago were not enrolled.. Written informed consent was obtained from the subject prior to enrolment in the extension study.

Number of Subjects:	**HAV Group**	**HPV Group**
Planned, N	429	437
Entered, N (Total Vaccinated cohort M48 EXT-032)	377	375
Completed (Month 48), n (%)	348 (92.3)	358 (95.5)
Total Number Subjects Withdrawn, n (%)	29 (7.7)	17 (4.5)
Withdrawn due to Adverse Events n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not Applicable	Not Applicable
Withdrawn for other reasons n (%)	29 (7.7)	17 (4.5)
Demographics	**HAV Group**	**HPV Group**
N (Total Vaccinated Cohort M48 EXT-032)	377	375
Females: Males	377:0	375:0
Mean Age, years (SD)	25.5 (1.72)	25.4 (1.72)
Asian - Japanese heritage, n (%)	377 (100)	375 (100)

Primary Efficacy Results: Incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy M48 EXT-032)

					Person-year rate			**VE**			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	332	0	273.69	0.00	0.00	1.35	100	-3.7	100	0.0616
	HAV	335	5	260.18	1.92	0.62	4.48	-	-	-	-
HPV-16	HPV	286	0	240.00	0.00	0.00	1.54	100	-0.4	100	0.0614
	HAV	289	5	220.83	2.26	0.74	5.28	-	-	-	-
HPV-18	HPV	294	0	242.95	0.00	0.00	1.52	.	.	.	-
	HAV	291	0	227.15	0.00	0.00	1.62	-	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at Month 36 / Month 48 in study HPV-063
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Secondary Outcome Variables: Incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

					Person-year rate			**VE**		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-16/18	HPV	406	0	1205.58	0.00	0.00	0.31	100	42.2	100
	HAV	404	8	1190.48	0.67	0.29	1.32	-	-	-
HPV-16	HPV	349	0	1039.53	0.00	0.00	0.35	100	31.5	100
	HAV	350	7	1026.21	0.68	0.27	1.41	-	-	-

HPV-18	HPV	357	0	1067.07	0.00	0.00	0.35	100	-3708.2	100
	HAV	354	1	1041.94	0.10	0.00	0.53	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against cytological abnormalities (ASC-US+) associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy Month 48 EXT-032)

					Person-year rate			VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-16/18	HPV	332	3	267.50	1.12	0.23	3.28	74.4	3.2	95.4
	HAV	335	11	250.83	4.39	2.19	7.85	-	-	-
HPV-16	HPV	286	2	235.11	0.85	0.10	3.07	81.9	14.9	98.1
	HAV	289	10	213.23	4.69	2.25	8.62	-	-	-
HPV-18	HPV	294	1	238.00	0.42	0.01	2.34	53.5	-793.8	99.2
	HAV	291	2	221.50	0.90	0.11	3.26	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at Month 36 / Month 48 in study HPV-063
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against cytological abnormalities (ASC-US+) associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

					Person-year rate			VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-16/18	HPV	406	4	1197.99	0.33	0.09	0.85	80.6	41.9	95.2
	HAV	403	20	1164.94	1.72	1.05	2.65	-	-	-
HPV-16	HPV	349	2	1034.65	0.19	0.02	0.70	87.8	48.3	98.6
	HAV	350	16	1007.00	1.59	0.91	2.58	-	-	-
HPV-18	HPV	357	2	1060.73	0.19	0.02	0.68	61.1	-137.6	96.3
	HAV	353	5	1031.57	0.48	0.16	1.13	-	-	-

ASC-US+ = ASC-US, LSIL, HSIL, ASC-H (Atypical Squamous Cell – cannot exclude HSIL) and AGC (Atypical Glandular Cells)
N=number of subjects included in each group.
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3

n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against cytological abnormalities (ASC-US+) associated with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline, using conditional exact method (ATP cohort for efficacy Month 48 EXT-032)

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	363	33	277.45	11.89	8.19	16.70	33.6	-6.3	59.0
	HAV	359	45	251.08	17.92	13.07	23.98	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at Month 36 / Month 48 in study HPV-063
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against cytological abnormalities (ASC-US+) associated with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	444	54	1249.68	4.32	3.25	5.64	26.7	-6.1	49.6
	HAV	433	70	1188.16	5.89	4.59	7.44	-	-	-

ASC-US+ = ASC-US, LSIL, HSIL, ASC-H (Atypical Squamous Cell – cannot exclude HSIL) and AGC (Atypical Glandular Cells)
N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against CIN1+ associated with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline (ATP cohort for efficacy Month 48 EXT-032)

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	363	8	295.26	2.71	1.17	5.34	66.4	21.6	87.1
	HAV	359	22	273.14	8.05	5.05	12.19	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at Month 36 / Month 48 in study HPV-063

n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against CIN1+ associated with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	444	13	1304.85	1.00	0.53	1.70	63.4	28.8	82.3
	HAV	435	34	1249.69	2.72	1.88	3.80	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against incident infection with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy Month 48 EXT-032)

					Person-year rate			VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-16/18	HPV	332	7	263.72	2.65	1.07	5.47	77.4	47.1	91.7
	HAV	335	28	238.20	11.75	7.81	16.99	-	-	-
HPV-16	HPV	286	3	234.25	1.28	0.26	3.74	83.4	41.9	96.9
	HAV	289	16	207.66	7.71	4.40	12.51	-	-	-
HPV-18	HPV	294	5	234.22	2.13	0.69	4.98	64.8	-5.3	90.2
	HAV	291	13	214.44	6.06	3.23	10.37	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at Month 36 / Month 48 in study HPV-063
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method);
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against incident infection with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

					Person-year rate			VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-16/18	HPV	406	12	1186.73	1.01	0.52	1.77	80.8	63.9	90.6
	HAV	403	58	1100.77	5.27	4.00	6.81	-	-	-
HPV-16	HPV	349	7	1026.75	0.68	0.27	1.40	79.8	53.5	92.4
	HAV	350	33	979.75	3.37	2.32	4.73	-	-	-
HPV-18	HPV	357	8	1057.27	0.76	0.33	1.49	73.1	39.4	89.4
	HAV	353	28	995.72	2.81	1.87	4.06	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type

For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against incident infection with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline (ATP cohort for efficacy Month 48 EXT-032)

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	363	87	246.95	35.23	28.22	43.46	22.2	-5.0	42.4
	HAV	359	98	216.48	45.27	36.75	55.17	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at Month 36 / Month 48 in study HPV-063
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method);
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against incident infection with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	444	145	1071.79	13.53	11.42	15.92	24.4	5.2	39.7
	HAV	433	175	978.52	17.88	15.33	20.74	-	-	-

N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against persistent infection (12-month definition) with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy Month 48 EXT-032)

					Person-year rate			VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-16/18	HPV	257	0	243.50	0.00	0.00	1.51	100	54.3	100
	HAV	241	9	219.64	4.10	1.87	7.78	-	-	-
HPV-16	HPV	225	0	213.51	0.00	0.00	1.73	100	25.0	100
	HAV	206	6	188.65	3.18	1.17	6.92	-	-	-
HPV-18	HPV	227	0	215.33	0.00	0.00	1.71	100	-36.2	100
	HAV	209	4	193.62	2.07	0.56	5.29	-	-	-

N=number of subjects included in each group
Persistent infection (12-month definition): Subjects with at least two positive samples (difference larger than 300 days) and no negative samples in between
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at Month 36 / Month 48 in study HPV-063
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against persistent infection (12-month definition) with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

					Person-year rate			VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-16/18	HPV	382	0	1185.30	0.00	0.00	0.31	100	74.8	100
	HAV	383	16	1149.98	1.39	0.80	2.26	-	-	-
HPV-16	HPV	329	0	1022.47	0.00	0.00	0.36	100	65.0	100
	HAV	331	12	995.28	1.21	0.62	2.11	-	-	-
HPV-18	HPV	338	0	1050.29	0.00	0.00	0.35	100	-5.8	100
	HAV	335	5	1018.59	0.49	0.16	1.15	-	-	-

N=number of subjects included in each group
Subjects had at least 10 months of follow-up after Month 12
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against persistent infection (12-month definition) with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline, using conditional exact method (ATP cohort for efficacy Month 48 EXT-032)

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	280	19	247.49	7.68	4.62	11.99	46.1	1.6	71.3
	HAV	261	31	217.50	14.25	9.68	20.23	-	-	-

N=number of subjects included in each group
Persistent infection (12-month definition): Subjects with at least 2 positive samples (difference larger than 300 days) and no negative samples in between
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at Month 36 / Month 48 in study HPV-063
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method);
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Incidence rates and vaccine efficacy against persistent infection (12-month definition) with any oncogenic HPV type by (PCR) in HPV DNA negative subjects at baseline, using conditional exact method (ATP cohort for efficacy (pooled))

				Person-year rate				VE		
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**
HPV-HR	HPV	419	34	1237.32	2.75	1.90	3.84	39.4	5.0	61.8
	HAV	413	53	1168.64	4.54	3.40	5.93	-	-	-

N=number of subjects included in each group
Subjects had at least 10 months of follow-up after Month 12
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative for the corresponding HPV type at Month 0 and Month 6
HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method);
LL,UL=95% Lower and Upper confidence limits

Secondary Outcome Variables: Seropositivity rates and GMTs for HPV-16 antibody titres (ATP cohort for immunogenicity M48 EXT-032)

					≥ 8 EL.U/mL				GMT		
							95% CI			95% CI	
Antibody	**Group**	**Pre-vacc status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**Value**	**LL**	**UL**
HPV-16	HPV	S-	PRE	255	0	0.0	0.0	1.4	4.0	4.0	4.0
			PII(M6)	255	255	100	98.6	100	641.1	580.4	708.2
			PIII(M7)	255	255	100	98.6	100	7857.8	7131.8	8657.7
			PIII(M12)	254	254	100	98.6	100	2875.5	2564.4	3224.3
			PIII(M18)	253	253	100	98.6	100	1824.3	1622.5	2051.3
			PIII(M24)	255	255	100	98.6	100	1531.4	1369.4	1712.6
			PIII(M36)	242	242	100	98.5	100	1388.5	1236.4	1559.4
			PIII(M48)	246	246	100	98.5	100	1283.2	1150.1	1431.7
		S+	PRE	47	47	100	92.5	100	29.3	21.5	39.8
			PII(M6)	47	47	100	92.5	100	1168.7	864.2	1580.5
			PIII(M7)	47	47	100	92.5	100	6031.7	4842.3	7513.2
			PIII(M12)	47	47	100	92.5	100	2769.2	2193.9	3495.3
			PIII(M18)	47	47	100	92.5	100	1951.5	1532.4	2485.1
			PIII(M24)	47	47	100	92.5	100	1579.8	1244.3	2005.9
			PIII(M36)	40	40	100	91.2	100	1546.4	1185.3	2017.4
			PIII(M48)	45	45	100	92.1	100	1359.9	1052.0	1758.0
		Total	PRE	302	47	15.6	11.7	20.2	5.5	5.0	6.0
			PII(M6)	302	302	100	98.8	100	703.9	637.8	776.9
			PIII(M7)	302	302	100	98.8	100	7540.9	6899.6	8241.9
			PIII(M12)	301	301	100	98.8	100	2858.6	2579.4	3168.0
			PIII(M18)	300	300	100	98.8	100	1843.7	1659.3	2048.6
			PIII(M24)	302	302	100	98.8	100	1538.9	1391.1	1702.3
			PIII(M36)	282	282	100	98.7	100	1409.9	1268.1	1567.6
			PIII(M48)	291	291	100	98.7	100	1294.8	1171.4	1431.1

S- = seronegative subjects (antibody concentration < 8 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 8 EL.U/mL) prior to vaccination
GMT = geometric mean titres concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = Pre-vaccination blood sample
PII(M6) = Post Dose II blood sample at Month 6
PIII(M7) = Post Dose III blood sample at Month 7
PIII(M12) = Post Dose III blood sample at Month 12
PIII(M18) = Post Dose III blood sample at Month 18
PIII(M24) = Post Dose III blood sample at Month 24
PIII(M36) = Post Dose III blood sample at Month 36
PIII(M48) = Post Dose III blood sample at Month 48

Secondary Outcome Variables: Seropositivity rates and GMTs for HPV-18 antibody titres (ATP cohort for immunogenicity M48 EXT-032)

					≥ 7 EL.U/mL				GMT		
							95% CI			95% CI	
Antibody	**Group**	**Pre-vacc status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
HPV-18	HPV	S-	PRE	259	0	0.0	0.0	1.4	3.5	3.5	3.5
			PII(M6)	259	259	100	98.6	100	476.7	429.7	529.0
			PIII(M7)	259	259	100	98.6	100	3983.7	3614.5	4390.7
			PIII(M12)	258	258	100	98.6	100	1316.5	1170.6	1480.5
			PIII(M18)	257	257	100	98.6	100	758.6	666.8	863.1
			PIII(M24)	259	259	100	98.6	100	620.8	549.4	701.4
			PIII(M36)	243	243	100	98.5	100	577.0	504.6	659.7
			PIII(M48)	250	250	100	98.5	100	473.0	416.8	536.8
		S+	PRE	42	42	100	91.6	100	17.5	12.9	23.7
			PII(M6)	42	42	100	91.6	100	592.2	442.5	792.6
			PIII(M7)	42	42	100	91.6	100	2960.3	2396.5	3656.8
			PIII(M12)	42	42	100	91.6	100	1131.6	882.8	1450.5
			PIII(M18)	42	42	100	91.6	100	673.8	510.8	888.9
			PIII(M24)	42	42	100	91.6	100	566.8	424.9	756.2
			PIII(M36)	38	38	100	90.7	100	543.0	387.1	761.7
			PIII(M48)	40	40	100	91.2	100	457.9	338.2	619.9
		Total	PRE	301	42	14.0	10.2	18.4	4.4	4.1	4.7
			PII(M6)	301	301	100	98.8	100	491.4	445.5	542.0
			PIII(M7)	301	301	100	98.8	100	3822.1	3496.3	4178.2
			PIII(M12)	300	300	100	98.8	100	1288.9	1158.7	1433.7
			PIII(M18)	299	299	100	98.8	100	746.1	663.7	838.7
			PIII(M24)	301	301	100	98.8	100	612.9	548.0	685.6
			PIII(M36)	281	281	100	98.7	100	572.3	505.6	647.7
			PIII(M48)	290	290	100	98.7	100	470.9	419.2	528.9

S- = seronegative subjects (antibody concentration < 7 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 7 EL.U/mL) prior to vaccination
GMT = geometric mean titres concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination blood sample;
PII(M6) = Post Dose II blood sample at Month 6
PIII(M7) = Post Dose III blood sample at Month 7
PIII(M12) = Post Dose III blood sample at Month 12
PIII(M18) = Post Dose III blood sample at Month 18
PIII(M24) = Post Dose III blood sample at Month 24
PIII(M36) = Post Dose III blood sample at Month 36
PIII(M48) = Post Dose III blood sample at Month 48

Secondary Outcome Variables: Number (%) of subjects with NOCDs during the follow-up period Month 24-Month 48 (Total Vaccinated Cohort M48 EXT-032)

NOCDs	**HPV Group N = 375**	**HAV Group N = 377**
Subjects with any NOCD(s), n (%)	2 (0.5)	2 (0.5)

Allergic granulomatous angiitis	1 (0.3)	-
Asthma	-	1 (0.3)
Multiple sclerosis	1 (0.3)	-
Still's disease adult onset	-	1 (0.3)

-: NOCD absent

Secondary Outcome Variables: Number (%) of subjects with NOADs during the follow-up period Month 24-Month 48 (Total Vaccinated Cohort M48 EXT-032)

NOADs	**HPV Group N = 375**	**HAV Group N = 377**
Subjects with any NOAD(s), n (%)	2 (0.5)	1 (0.3)
Multiple sclerosis	1 (0.3)	-
Allergic granulomatous angiitis	1 (0.3)	-
Still's disease adult onset	-	1 (0.3)

-: NOAD absent

Secondary Outcome Variables: Number (%) of subjects with NOCDs during the entire follow-up period Month 0- Month 48 (Total Vaccinated Cohort (pooled))

NOCDs	**HPV Group N = 519**	**HAV Group N = 521**
Subjects with any NOCD(s), n (%)	6 (1.2)	8 (1.5)
Urticaria	2 (0.4)	4 (0.8)
Asthma	2 (0.4)	1 (0.2)
Allergic granulomatous angiitis	1 (0.2)	-
Drug eruption	-	1 (0.2)
Multiple sclerosis	1 (0.2)	-
Rheumatoid arthritis	1 (0.2)	-
Rhinitis allergic	-	1 (0.2)
Still's disease adult onset	-	1 (0.2)

-: NOCD absent

Secondary Outcome Variables: Number (%) of subjects with NOADs during the entire follow-up period Month 0-Month 48 (Investigator assessment) (Total Vaccinated Cohort (pooled))

NOADs	**HPV Group N = 519**	**HAV Group N = 521**
Subjects with any NOAD(s), n (%)	3 (0.6)	1 (0.2)
Allergic granulomatous angiitis	1 (0.2)	-
Multiple sclerosis	1 (0.2)	-
Rheumatoid arthritis	1 (0.2)	-
Still's disease adult onset	-	1 (0.2)

-: NOAD absent

Secondary Outcome Variables: Number (%) of subjects with medically significant conditions (MSCs) during the follow-up period Month 24-Month 48 (Total Vaccinated Cohort M48 EXT-032)

MSCs	**HPV Group N = 375**	**HAV Group N = 377**
Subjects with any MSC(s), n (%)	11 (2.9)	15 (4.0)
Abortion missed	2 (0.5)	3 (0.8)
Foetal distress syndrome	-	2 (0.5)
Premature separation of placenta	2 (0.5)	-
Abortion spontaneous complete	1 (0.3)	-
Abortion spontaneous incomplete	-	1 (0.3)
Allergic granulomatous angiitis	1 (0.3)	-
Benign ovarian tumour	-	1 (0.3)
Borderline personality disorder	1 (0.3)	-
Cholelithiasis	-	1 (0.3)
Disseminated intravascular coagulation	1 (0.3)	-
Ectopic pregnancy	-	1 (0.3)
Foetal growth restriction	-	1 (0.3)
Gestational hypertension	1 (0.3)	-

Intra-uterine death	1 (0.3)	-
Intraocular pressure increased	1 (0.3)	-
Mastitis	-	1 (0.3)
Multiple sclerosis	1 (0.3)	-
Pneumonia influenzal	-	1 (0.3)
Pneumonia mycoplasmal	-	1 (0.3)
Premature labour	-	1 (0.3)
Still's disease adult onset	-	1 (0.3)
Threatened labour	1 (0.3)	-
Urticaria	1 (0.3)	-
Ventricular septal defect	-	1 (0.3)

-: MSC absent.

Secondary Outcome Variables: Number (%) of subjects with medically significant conditions (MSCs) during the follow-up period Month 0-Month 48 (Total Vaccinated Cohort (pooled))

MSCs	**HPV Group N = 519**	**HAV Group N = 521**
Subjects with any MSC(s), n (%)	98 (18.9)	115 (22.1)
Cystitis	4 (0.8)	9 (1.7)
Abortion missed	3 (0.6)	3 (0.6)
Abortion spontaneous	3 (0.6)	3 (0.6)
Eczema	3 (0.6)	3 (0.6)
Oropharyngeal pain	3 (0.6)	3 (0.6)
Urticaria	3 (0.6)	3 (0.6)
Enterocolitis	-	5 (1.0)
Acne	4 (0.8)	-
Bronchitis	4 (0.8)	-
Candidiasis	-	4 (0.8)
Asthma	3 (0.6)	-
Chlamydial infection	-	3 (0.6)
Dental caries	-	3 (0.6)
Depression	3 (0.6)	-
Dermatitis atopic	3 (0.6)	-
Genital herpes	3 (0.6)	-
Pyrexia	-	3 (0.6)

Counting rule applied: As there were more than 30 subjects per treatment group and ≤ 3 groups, only the 10 most frequent events in each treatment group are to be listed.
-: Implies that adverse event was not reported in the particular group or that the adverse event was reported in the particular group but did not fall within the pre-defined counting rule of 10 most frequent events for that group.

Secondary Outcome Variables: Number (%) of subjects with pregnancies and their outcomes during the follow-up period Month 24 – Month 48 (Total Vaccinated Cohort M48 EXT-032)

		HPV Group N = 37		**HAV Group N = 41**	
Characteristics	**Categories**	**n**	**%**	**n**	**%**
Outcome	Live infant NO apparent congenital anomaly	28	75.7	30	73.2
	Live infant congenital anomaly	0	0.0	1	2.4
	Elective termination NO apparent congenital anomaly	4	10.8	3	7.3
	Spontaneous abortion NO apparent congenital anomaly	3	8.1	4	9.8
	Stillbirth NO apparent congenital anomaly	1	2.7	0	0.0
	Ectopic pregnancy	0	0.0	1	2.4
	Lost to follow up	0	0.0	2	4.9
	Pregnancy ongoing	1	2.7	0	0.0

N = number of pregnancies reported
n (%) = number (percentage) of pregnancies in a given category

Secondary Outcome Variables: Number (%) of subjects with pregnancies and their outcomes during the follow-up period

Month 0 – Month 48 (Total Vaccinated Cohort (pooled))					
		HPV Group N = 83		**HAV Group N = 84**	
Characteristics	**Categories**	**n**	**%**	**n**	**%**
Outcome	Live infant NO apparent congenital anomaly	52	62.7	53	63.1
	Live infant congenital anomaly	0	0.0	1	1.2
	Elective termination NO apparent congenital anomaly	18	21.7	19	22.6
	Spontaneous abortion NO apparent congenital anomaly	8	9.6	7	8.3
	Stillbirth NO apparent congenital anomaly	1	1.2	0	0.0
	Ectopic pregnancy	0	0.0	1	1.2
	Premature live infant NO apparent congenital anomaly	1	1.2	0	0.0
	Lost to follow up	1	1.2	3	3.6
	Pregnancy ongoing	2	2.4	0	0.0
N = number of pregnancies reported n (%) = number (percentage) of pregnancies in a given category					

Safety results: Number (%) of subjects with SAEs during the follow-up period Month 24 – Month 48 (Total Vaccinated Cohort M48 EXT-032)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	**HPV Group N = 375**	**HAV Group N = 377**
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	11 (2.9) [0]	16 (4.2) [0]
Abortion missed	2 (0.5) [0]	3 (0.8) [0]
Foetal distress syndrome	0 (0.0) [0]	2 (0.5) [0]
Premature separation of placenta	2 (0.5) [0]	0 (0.0) [0]
Abortion spontaneous complete	1 (0.3) [0]	0 (0.0) [0]
Abortion spontaneous incomplete	0 (0.0) [0]	1 (0.3) [0]
Allergic granulomatous angiitis	1 (0.3) [0]	0 (0.0) [0]
Appendicitis	0 (0.0) [0]	1 (0.3) [0]
Benign ovarian tumour	0 (0.0) [0]	1 (0.3) [0]
Borderline personality disorder	1 (0.3) [0]	0 (0.0) [0]
Cholelithiasis	0 (0.0) [0]	1 (0.3) [0]
Disseminated intravascular coagulation	1 (0.3) [0]	0 (0.0) [0]
Ectopic pregnancy	0 (0.0) [0]	1 (0.3) [0]
Foetal growth restriction	0 (0.0) [0]	1 (0.3) [0]
Gestational hypertension	1 (0.3) [0]	0 (0.0) [0]
Intra-uterine death	1 (0.3) [0]	0 (0.0) [0]
Intraocular pressure increased	1 (0.3) [0]	0 (0.0) [0]
Mastitis	0 (0.0) [0]	1 (0.3) [0]
Multiple sclerosis	1 (0.3) [0]	0 (0.0) [0]
Pneumonia influenzal	0 (0.0) [0]	1 (0.3) [0]
Pneumonia mycoplasmal	0 (0.0) [0]	1 (0.3) [0]
Premature labour	0 (0.0) [0]	1 (0.3) [0]
Still's disease adult onset	0 (0.0) [0]	1 (0.3) [0]
Threatened labour	1 (0.3) [0]	0 (0.0) [0]
Urticaria	1 (0.3) [0]	0 (0.0) [0]
Ventricular septal defect	0 (0.0) [0]	1 (0.3) [0]
Fatal SAEs	**HPV Group N = 375**	**HAV Group N = 377**
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Safety results: Number (%) of subjects with SAEs during the follow-up period Month 0 – Month 48 (Total Vaccinated Cohort (pooled))
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs	**HPV Group N = 519**	**HAV Group N = 521**
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	26 (5.0) [1]	34 (6.5) [0]
Abortion missed	3 (0.6) [0]	3 (0.6) [0]
Abortion spontaneous	3 (0.6) [1]	3 (0.6) [0]
Appendicitis	1 (0.2) [0]	2 (0.4) [0]
Threatened labour	2 (0.4) [0]	1 (0.2) [0]
Abortion spontaneous incomplete	1 (0.2) [0]	1 (0.2) [0]
Abortion threatened	1 (0.2) [0]	1 (0.2) [0]
Acute tonsillitis	0 (0.0) [0]	2 (0.4) [0]
Foetal distress syndrome	0 (0.0) [0]	2 (0.4) [0]
Hepatitis acute	1 (0.2) [0]	1 (0.2) [0]
Premature separation of placenta	2 (0.4) [0]	0 (0.0) [0]
Abortion spontaneous complete	1 (0.2) [0]	0 (0.0) [0]
Acute abdomen	0 (0.0) [0]	1 (0.2) [0]
Allergic granulomatous angiitis	1 (0.2) [0]	0 (0.0) [0]
Avulsion fracture	0 (0.0) [0]	1 (0.2) [0]
Benign ovarian tumour	0 (0.0) [0]	1 (0.2) [0]
Borderline personality disorder	1 (0.2) [0]	0 (0.0) [0]
Brain contusion	1 (0.2) [0]	0 (0.0) [0]
Cholelithiasis	0 (0.0) [0]	1 (0.2) [0]
Completed suicide	1 (0.2) [0]	0 (0.0) [0]
Contusion	0 (0.0) [0]	1 (0.2) [0]
Depression	1 (0.2) [0]	0 (0.0) [0]
Disseminated intravascular coagulation	1 (0.2) [0]	0 (0.0) [0]
Ectopic pregnancy	0 (0.0) [0]	1 (0.2) [0]
Enterocolitis	0 (0.0) [0]	1 (0.2) [0]
Eyeball rupture	1 (0.2) [0]	0 (0.0) [0]
Fatigue	0 (0.0) [0]	1 (0.2) [0]
Foetal growth restriction	0 (0.0) [0]	1 (0.2) [0]
Gastritis	0 (0.0) [0]	1 (0.2) [0]
Gestational hypertension	1 (0.2) [0]	0 (0.0) [0]
Intra-uterine death	1 (0.2) [0]	0 (0.0) [0]
Intraocular pressure increased	1 (0.2) [0]	0 (0.0) [0]
Ligament injury	1 (0.2) [0]	0 (0.0) [0]
Ligament rupture	0 (0.0) [0]	1 (0.2) [0]
Mastitis	0 (0.0) [0]	1 (0.2) [0]
Mastitis postpartum	0 (0.0) [0]	1 (0.2) [0]
Moyamoya disease	0 (0.0) [0]	1 (0.2) [0]
Multiple sclerosis	1 (0.2) [0]	0 (0.0) [0]
Ovarian haemorrhage	1 (0.2) [0]	0 (0.0) [0]
Panic disorder	1 (0.2) [0]	0 (0.0) [0]
Pneumonia	0 (0.0) [0]	1 (0.2) [0]
Pneumonia influenzal	0 (0.0) [0]	1 (0.2) [0]
Pneumonia mycoplasmal	0 (0.0) [0]	1 (0.2) [0]
Pneumothorax	1 (0.2) [0]	0 (0.0) [0]
Polycystic ovaries	0 (0.0) [0]	1 (0.2) [0]
Premature labour	0 (0.0) [0]	1 (0.2) [0]
Pyelonephritis acute	1 (0.2) [0]	0 (0.0) [0]
Road traffic accident	1 (0.2) [0]	0 (0.0) [0]
Schizophrenia	0 (0.0) [0]	1 (0.2) [0]
Skull fracture	1 (0.2) [0]	0 (0.0) [0]
Still's disease adult onset	0 (0.0) [0]	1 (0.2) [0]
Urticaria	1 (0.2) [0]	0 (0.0) [0]
Ventricular septal defect	0 (0.0) [0]	1 (0.2) [0]
Fatal SAEs	**HPV Group**	**HAV Group**

	N = 519	N = 521
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	1 (0.2) [0]	0 (0.0) [0]
Completed suicide*	1 (0.2) [0]	0 (0.0) [0]
* This fatal SAE was reported during the HPV-032 study period.		

Conclusion:
During the HPV-063 follow-up study period (12 months), the HPV vaccine efficacy in the prevention of histopathologically confirmed CIN1+ associated with HPV-16/18 infection was 100% (95% CI: -3.7% to 100%; 5 cases, all in the HAV Group) in adult Japanese women who were, for the corresponding HPV type, seronegative (by ELISA) at Month 0 and HPV DNA negative (by PCR) at Months 0 and 6 in the primary study HPV-032.
During the entire follow-up period from the beginning of study HPV-032 till the end of the extension study HPV-063, 60 subjects reported 74 SAEs, 36 SAEs in 26 subjects in the HPV group and 38 SAEs in 34 subjects in the HAV group. One SAE (Abortion spontaneous) in the HPV Group was assessed by the investigator as related to the study vaccination. One fatal SAE (completed suicide) was reported in the HPV Group; it was assessed by the investigator as not related to the study vaccination. Both SAEs occurred during study HPV-032.
During the follow-up period from the end of study HPV-032 till the end of the extension study HPV-063, 27 subjects reported 31 SAEs, 14 SAEs in 11 subjects in the HPV group and 17 SAEs in 16 subjects in the HAV group. No fatal SAEs or SAEs assessed by the investigators as possibly related to vaccination were reported.
For safety data about the primary study, please refer to the HPV-032 CTRS.

Publications: None

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