Statistical Analysis Plan

Study alias & e-track number(s): HPV-094 (207644)

Analysis ID / Description: ANALYSIS_E1_01 (SRT analysis to investigate the imbalance in CIN cases)

Detailed Title:	Meta analysis of HPV-associated cases in efficacy studies according to baseline cytology and DNA status.
SAP version	Version 1
SAP date	30-Jan-2017
Scope:	Efficacy data related to the studies HPV-008, HPV-015, HPV-032, HPV-063 Ext HPV-032, HPV-039
Co-ordinating author:	[redacted] (Lead Statistician)
Requestor	[redacted] (CRDL)
Date of Database Freeze (DBF)	Respective DBF dates for each of the study
Approved by:	[redacted] (CEPL), [redacted] (Statistician), [redacted] (Lead Statistician), [redacted] (CRDL), [redacted](Safety Physician) [redacted] (Regulatory)

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1. DOCUMENT HISTORY

Date	Description	Protocol Version
30-Jan-2017	Version 1	NA

2. RATIONALE

This analysis is performed following the outcome of discussion in the HPV SRT about the imbalance observed in the incidence of CIN2+ and CIN3+ in HPV-015 study: more CIN2+ cases were accrued in the vaccine group in subjects with high grade cytology and DNA positive at baseline. This was noticed while preparing a response to questions received by EMA on the submission for HPV-015 study and was decided to investigate further by looking to other efficacy studies including younger subjects (<25 years) and pooled.

3. STUDY DESIGN

Studies included are,

- HPV-008
- HPV-015
- HPV-039
- HPV-032

HPV-008:

HPV-008 is a phase III, double-blind, randomized, and controlled study with two parallel groups. The study was conducted in Asia Pacific, Europe, Latin America and North America. Women aged 15 to 25 years (N = ~18,000) were enrolled in the study. Subjects received three doses of HPV-16/18 Vaccine or control (Hepatitis A virus (HAV) vaccine) at 0, 1, 6 months according to their random assignment (1:1 randomization).

The study was designed to evaluate vaccine efficacy in the prevention of CIN2+ lesions associated with HPV-16 or HPV-18 infection (CIN2+ includes CIN2, CIN3, endocervical adenocarcinoma *in situ* (AIS) and invasive cervical cancer) in adolescents and young adult women, 15-25 years of age, during the 42 months following the administration of three doses of HPV-16/18 VLP/AS04 vaccine.

For more information on the design, methods and results please refer to the following publications:

- Lehtinen M, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012 Jan;13(1):89-99. [1]

- Wheeler CM, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012 Jan;13(1):100-10. [2]
- Paavonen J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women. Lancet. 2009 Jul 25;374(9686):301-14. [3]
- Paavonen J, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet. 2007 Jun 30;369(9580):2161-70. [4]

HPV-015:

A phase III, double-blind, randomised, controlled study to evaluate the safety, immunogenicity and efficacy of GlaxoSmithKline Biologicals' HPV-16/18 L1 AS04 vaccine administered intramuscularly according to a three-dose schedule (0, 1, 6 month) in healthy adult female subjects aged 26 years and above.

The study was designed to evaluate vaccine efficacy in the prevention of 6-month PI and/or CIN1+ lesions associated with HPV-16 or HPV-18 infection in healthy adult female subjects aged 26 years and above, during the 84 months following the administration of three doses of HPV-16/18 VLP/AS04 vaccine.

For more information on the design, methods and results please refer to the following publications:

- Skinner SR, Szarewski A, Romanowski B et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. The Lancet 2014; 384(9961):2213-27.

- Wheeler, CM, Skinner, SR, Del Rosario-Raymundo, MR et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet Infect Dis. 2016; 16: 1154–1168

HPV-039:

A phase II/III, double-blind, randomised, controlled study to evaluate the efficacy, immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy Chinese female subjects aged 18-25 years.

The study was designed to evaluate vaccine efficacy in the prevention of 6-month PI and/or CIN1+ lesions associated with HPV-16 or HPV-18 infection in healthy adult female subjects aged 18-25 years, during the 72 months following the administration of three doses of HPV-16/18 VLP/AS04 vaccine.

For more information on the design, methods and results please refer to the following publications:

- Zhu F, Li J, Hu Y et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years: Results from 2 randomised controlled trials. Hum Vaccin Immunother. 2014;10 (7), 1795-1806.
- Zhu FC, Chen W, Hu YM et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: Results from a randomised controlled trial. Int J Cancer. 2014; 135(11), 2612-22.

HPV-032 & HPV-063 Ext HPV-039:

A double-blind (observer-blind), randomized, controlled, phase II study to assess the efficacy, immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy Japanese female subjects aged 20-25 years.

The study was designed to evaluate vaccine efficacy in the prevention of 6-month PI associated with HPV-16 or HPV-18 infection in healthy adult female subjects aged 20-25 years, during the 48 months following the administration of three doses of HPV-16/18 VLP/AS04 vaccine.

For more information on the design, methods and results please refer to the following publications:

- Konno R, Dobbelaere KO, Godeaux OO et al. Immunogenicity, reactogenicity, and safety of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women: interim analysis of a phase II, double-blind, randomized controlled trial at month 7. Int J Gynecol Cancer. 2009;19(5):905-11
- Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: interim analysis of a phase 2 double-blind, randomized, controlled trial. Int J Gynecol Cancer. 2010;20(3):404-10
- Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. Int J Gynecol Cancer. 2010;20(5):847-55

The following group names will be used for the pooled statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	HPV	Subjects receiving HPV-16/18 L1 VLP ASO4 Vaccine
2	Control	Subjects receiving the control vaccine

Subjects randomised to receive HPV vaccine in the studies HPV-008, HPV-015, HPV-039, HPV-032 will be pooled together and analysed as the 'HPV group' and subjects randomised to receive control vaccine in the studies will be pooled together and analysed as the 'Control group'.

To note that the control used in the studies may not be the same. Ex: in HPV-039 study, control used is Placebo containing Al(OH)3 & in HPV-008 study, control used is Hepatitis A Vaccine.

4. ANALYSIS SET

The Total Vaccinated Cohort (TVC) defined in the respective studies will be used for the analyses. In general, TVC is defined as subjects who received atleast one dose of the study vaccine in the study. The TVC analysis was performed per treatment actually administered. If any subjects are eliminated from all statistical analysis in the respective studies, those will not be included in this study analysis as well.

5. DESCRIPTION OF ANALYSIS

Following analysis will be performed,

- Demographic charecteristics will be presented by pooled studies (Table 1).
    - Analysis will also be performed by considering sub-groups: Cytology status at baseline (Normal, Low, high), HPV DNA status at baseline
- Overview of DNA status for subjects with cytology at baseline (Table 2),
    - Without HR,
    - With HR,
    - With HR without 16/18 (HRW),
    - With 16/18 only
- Overview of DNA status for subjects (By HPV types) with cytology at baseline will be provided as a listing.
- Summary table on incidence of cases of CIN2, CIN2+, CIN3+ in each group and study (Table 3).
    - The above analysis will also be performed by,
        - Cytology at baseline: normal, low grade (ASC-US+LSIL) or high grade (AGC+ASC-H+HSIL),
        - HR DNA at baseline & Cytology status (Normal/low/high).
        - Serology & DNA status at baseline
    - An xls will be generated for the above mentioned analysis to provide an overview of the data for each of the subjects with CIN2, CIN2+ & CIN3.
- Cumulative incidence of CIN2, CIN2+ and CIN3+ will be presented in the form of a graph (Figure 1).
    - This analysis will be performed by study and overall.
- Type distribution for CIN2, CIN2+ and CIN3+ cases will be provided overall and by cytology status at baseline (Normal/Low/High) (Table 4).

The above analysis may be performed by age group (15-17; 18-20; 15-20; 21-25 years), if there are enough cases.

6. INTERPRETATION OF STATISTICAL ANALYSIS

All analysis will be descriptive in nature with the intent to understand the differene in incidence of CIN cases. Interpretation from this analysis needs to be made carefully by considering that this is a post-hoc analysis and no formal sample size computations were done for evaluation of the study objectives.

7. TABLE AND FIGURE TEMPLATES

*These templates are for illustrative purpose only.

Table 1 Summary of demographic characteristics (Total vaccinated cohort)

		HPV N = xxx		Control N = xxx		Total N = xxx	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
Gender	Female						
Race	xxxx						
Height (cm)	Mean						
	SD						
	Median						
Weight (kg)	Mean						
	SD						
	Median						
BMI (kg/m²)	Mean						
	SD						
	Median						

N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Table 2 Overview of cytology status and HPV DNA status of subjects at baseline (Total vaccinated cohort)

	HPV		Control		Total	
Characteristics at Visit 1	**N**	**% of total**	**N**	**% of total**	**N**	**% of total**
Total vaccinated cohort						
Subjects with normal cytology						
Without HR-HPV						
With HR-HPV						
With HR-HPV other than vaccine type						
With HPV vaccine type HPV-16/18						
Subjects with low-grade cytology						
Without HR-HPV						
With HR-HPV						
With HR-HPV other than vaccine type						
With HPV vaccine type HPV-16/18						
Subjects with high-grade cytology						
Without HR-HPV						
With HR-HPV						
With HR-HPV other than vaccine type						
With HPV vaccine type HPV-16/18						

	HPV		Control		Total	
Characteristics at Visit 1	**N**	**% of total**	**N**	**% of total**	**N**	**% of total**
Subjects with missing cytology						

N = Number of subjects in each group
HR-HPV = High-risk HPV types
Normal cytology = negative or ASC-US/HCII-
Low-grade cytology = ASC-US/HCII+, ASC-US/HCII QNS or LSIL
High-grade cytology = HSIL, AGC or ASC-H

Table 3 Incidence of CIN2, CIN2+ & CIN3+ (TVC)

		HPV N = xxx		Control N = xxx		Total N = xxx	
Endpoint	**Cytology Status**	**n**	**%**	**n**	**%**	**n**	**%**
CIN2	Normal						
	Low						
	High						
	Total						
CIN2+	Normal						
	Low						
	High						
	Total						
CIN3+	Normal						
	Low						
	High						
	Total						

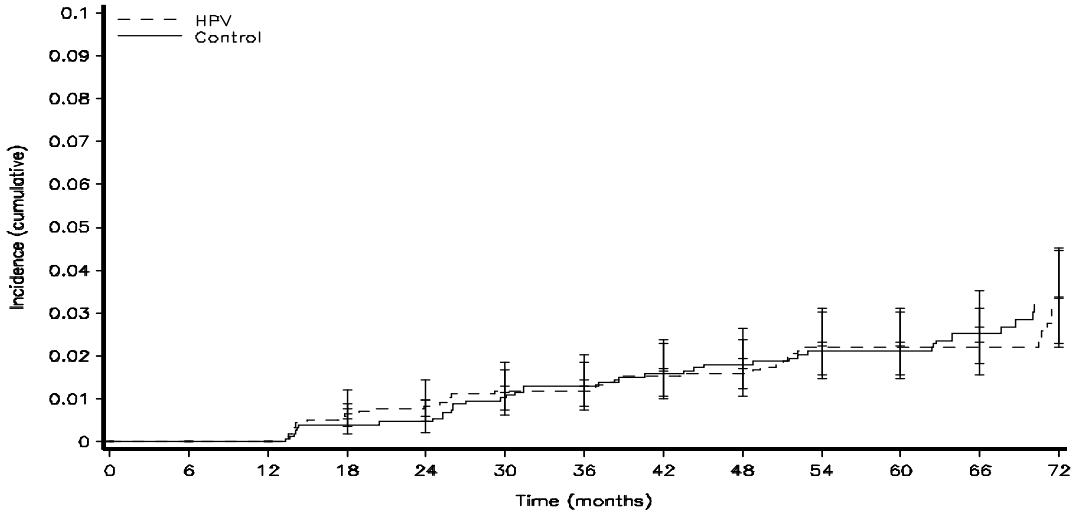
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Missing= subjects either DNA status or sero status missing at baseline

Table 4 Number of subjects reported CIN2, CIN2+ and CIN3+ cases associated with HPV-16/18 only, co-infections, no HPV-16/18 (TVC)

Category	CIN2		CIN2+		CIN3+	
	HPV N=	Control N=	HPV N=	Control N=	HPV N=	Control N=5452
	n	n	n	n	n	n
With HR-HPV						
Withour HR-HPV						
With HR-HPV other than vaccine type						
With HPV vaccine type HPV-16/18						

N = Number of subjects included in each group
n = Number of subjects reporting event in the corresponding category in each group

Figure 1 Cumulative incidence curve for CIN2, CIN2+, CIN3+, truncated at Month X (TVC)



Number at risk

HPV	1591	1590	1563	1530	1498	1465	1450	1421	1365	1269	1227	1065	498
Control	1530	1530	1508	1487	1461	1418	1398	1377	1330	1236	1187	1007	509

Cumulative number of cases

HPV	0	0	0	10	13	18	18	23	24	32	32	32	37
Control	0	0	0	6	7	15	19	23	26	30	30	35	39