25 January 2018
EMA/100422/2018
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cervarix

human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)

Procedure no: EMEA/H/C/000721/P46/093

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Final report Study MenACWY-TT-054:

A Phase III, open, randomised, controlled, multicentre (Estonia, Thailand, Dominican Republic) study to assess the immunogenicity and reactogenicity of GSK Biologicals' meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (MenACWY-TT [Nimenrix]) administered alone as compared to MenACWY-TT co-administered with GSK Biologicals' HPV vaccine Cervarix or co-administered with Cervarix and GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap [Boostrix]) in female adolescents and young adults at 9-25 years of age.

This is an Art 46 submission of a Nimenrix study in which Cervarix is co-administered. No SmPC modifications are proposed by the MAH.

1.1. Steps taken for the assessment

Submission date:	31/08/2017
Start of procedure:	27/11/2017
CHMP Rapporteur's preliminary assessment report circulated on:	03/01/2018
CHMP Rapporteur's updated assessment report circulated on:	18/01/2018
CHMP opinion:	25/01/2018

2. Assessment of the post-authorisation measure PAM MenACWY-TT-054

Based on the epidemiology of disease caused by N. meningitidis and Bordetella pertussis, adolescents stand to benefit from vaccination against both pathogens. Co-administration of MenACWY-TT with Boostrix (Tdap) was evaluated in male and female subjects aged between 11 and 25 years (adolescents and adults) in a separate clinical study. The current study evaluated co-administration of MenACWY-TT, Cervarix and Boostrix as compared to administration of MenACWY-TT and Cervarix vaccines alone in females from 9 to 25 years of age. Co-administration of the three vaccines may contribute to improve the implementation and coverage of adolescent vaccination programmes.

STUDY OBJECTIVES

The co-primary objectives were assessed in hierarchical manner according to the order presented below. A co-primary objective could only be met if the statistical criteria for that objective as well as the statistical criteria for all previous co-primary objectives were met.

Co-primary objectives

To demonstrate the non-inferiority of MenACWY-TT co-administered with Cervarix compared to MenACWY-TT alone with respect to serum bactericidal assay (using baby rabbit complement, rSBA) geometric mean titres (GMTs) for serogroups A, C, W-135 and Y one month after MenACWY-TT vaccination.

Non-inferiority criterion: For each serogroup separately, one month after vaccination with MenACWY-TT, the upper limit (UL) of the two-sided standardised asymptotic 95% confidence interval (CI) for the ratio of rSBA GMTs (ACWY-TT group/ACWYHPV group) was < the pre-defined limit of 2.

To demonstrate the non-inferiority of Cervarix co-administered with MenACWY-TT compared to Cervarix alone in terms of human papilloma virus 16 (HPV16) and HPV18 GMTs as measured by enzyme linked immunosorbent assay (ELISA) one month after the third dose of Cervarix.

Non-inferiority criterion: For each HPV antigen separately (HPV16 and HPV18), one month after the third dose of Cervarix, the UL of the two-sided standardised asymptotic 95% CI on the group GMT ratio (HPV group/ACWYHPV group) was < the pre-defined limit of 2.

To demonstrate the non-inferiority of MenACWY-TT co-administered with Cervarix and Boostrix compared to MenACWY-TT alone with respect to rSBA GMTs for serogroups A, C, W-135 and Y one month after MenACWY-TT vaccination.

Non-inferiority criterion: For each serogroup separately, one month after vaccination with MenACWY-TT, the UL of the two sided standardised asymptotic 95% CI for the ratio of rSBA GMTs (ACWY-TT group/Co-ad group) was < the pre-defined limit of 2.

To demonstrate the non-inferiority of Cervarix co-administered with MenACWY-TT and Boostrix compared to Cervarix co-administered with Boostrix in terms of HPV16 and HPV18 GMTs as measured by ELISA one month after the third dose of Cervarix.

Non-inferiority criterion: For each HPV antigen separately (HPV16 and HPV18), one month after the third dose, the UL of the two-sided standardised asymptotic 95% CI on the group GMT ratio (Tdap group/Co-ad group) was < the pre-defined limit of 2.

To demonstrate the non-inferiority of Boostrix co-administered with MenACWY-TT and Cervarix compared to Boostrix co-administered with Cervarix in terms of antibody concentrations against diphtheria toxoid (anti-D) and tetanus toxoid (anti-T) one month after Boostrix vaccination.

Non-inferiority criterion: The lower limit (LL) of the two-sided standardised asymptotic 95% CI for the group difference (Co-ad group minus Tdap group) in the percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL was ≥ the pre-defined limit of -10%. and the LL of the two-sided standardised asymptotic 95% CI for the group difference (Co-ad group minus Tdap group) in the percentage of subjects with anti-T antibody concentrations ≥1.0 IU/mL was ≥ the pre-defined limit of -10%.

To demonstrate the non-inferiority of Boostrix co-administered with MenACWY-TT and Cervarix compared to Boostrix co-administered with Cervarix with respect to Geometric mean concentration (GMC) to each discrete pertussis antigen (pertussis toxoid [PT], filamentous hemagglutinin [FHA] and pertactin [PRN]) one month after Boostrix vaccination.

Non-inferiority criterion: For each discrete pertussis antigen (PT, FHA and PRN), the UL of the two-sided 95% CI for the group ratio of GMC (Tdap group / Co-ad group) was ≤ the predefined limit of 1.5.

Secondary objectives

Immunogenicity

Prior to and one month after vaccination with MenACWY-TT

- To evaluate the immunogenicity of subjects in the ACWYHPV, ACWY-TT and Coad groups in terms of percentage of subjects with rSBA titres ≥1:8, ≥1:128 and vaccine response one month post-vaccination.
- To evaluate the immunogenicity of the TT carrier protein in the ACWY-TT group in terms of the percentage of subjects with anti-T concentrations ≥0.1 IU/mL, ≥1.0 IU/mL and GMCs. Prior to the first dose of Cervarix and one month after the third dose of Cervarix
- To evaluate the immunogenicity of Cervarix in subjects in the ACWYHPV, HPV, Co-ad, ACWY-TT and Tdap groups with respect to the percentage of subjects with titres ≥19 EL.U/mL for anti-HPV16 and ≥18 EL.U/mL for anti-HPV18.
- To evaluate the immunogenicity of subjects in the ACWY-TT group with respect to HPV16 and HPV18 GMTs.
- To evaluate the immunogenicity of the ACWYHPV, ACWY-TT, HPV, Co-ad and Tdap groups with respect to seroconverstion rates of anti-HPV16 and anti-HPV18 titres one month post dose 3. Prior to and one month after vaccination with Boostrix
- To evaluate the booster responses to PT, FHA and PRN in the Co-ad and Tdap groups.
- To evaluate the immunogenicity of Boostrix in the Co-ad and Tdap groups in terms of percentage of subjects with anti-D and anti-T concentrations ≥0.1 IU/mL, anti-PT, anti-FHA and anti-PRN concentrations ≥ the assay cut-offs and GMCs.

Exploratory objectives

The exploratory objectives were related to the comparability of the study vaccine versus the control vaccines in terms of immune response to the different vaccine antigens one month after the vaccination with MenACWY-TT and one month after the third dose Cervarix vaccination.

These group comparisons are exploratory and any potential differences should be interpreted with caution considering that there was no adjustment for multiplicity of comparisons and that the clinical relevance of any differences remains unknown.

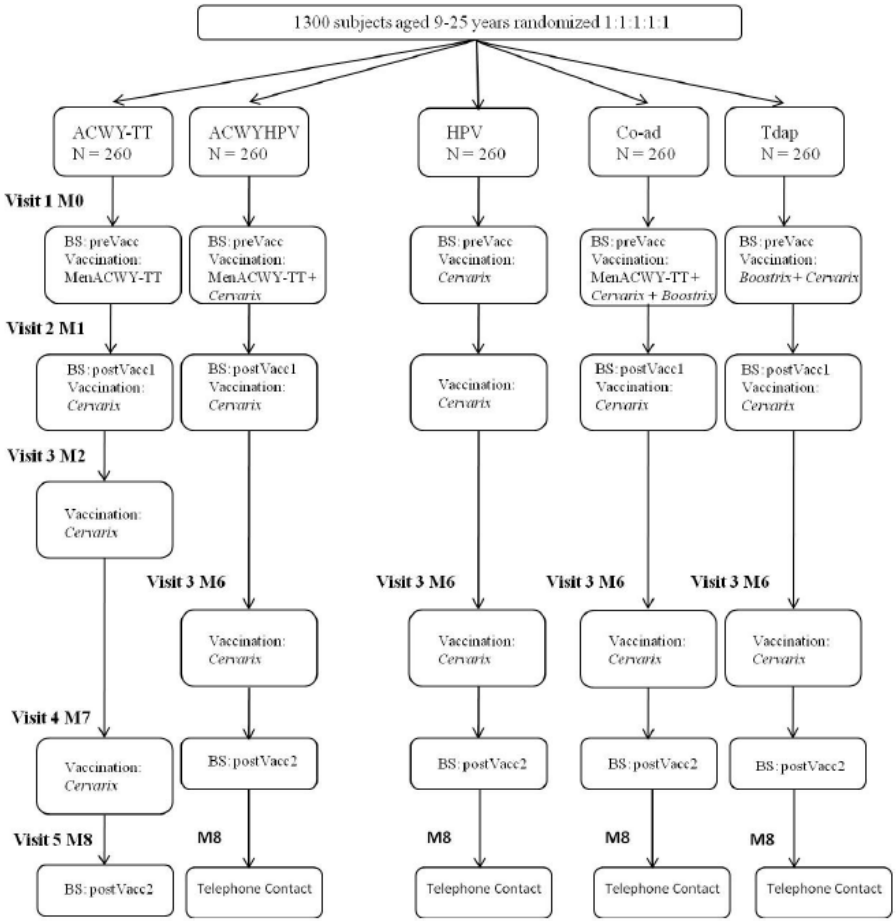
Safety and reactogenicity

To evaluate the safety and reactogenicity after vaccination with MenACWY-TT, Boostrix and Cervarix in all groups:

- Solicited local and general Adverse events (AEs): - Days 0-6 following vaccination with MenACWY-TT administered alone or coadministered with Cervarix or Cervarix + Boostrix. - Days 0-6 after Dose 1 of Cervarix administered alone or co-administered with MenACWY-TT or MenACWY-TT + Boostrix, - Days 0-6 following vaccination with Boostrix co-administered with Cervarix or with Cervarix + MenACWY-TT.
- Unsolicited symptoms on Days 0-30 after vaccination with MenACWY-TT, the first dose of Cervarix and/or Boostrix in all groups.
- Serious adverse events (SAEs) and new onset of chronic illness(es) (NOCIs, e.g. autoimmune disorders, asthma, type 1 diabetes and allergies) and Potential immunemediated diseases (pIMDs) from first vaccination through study end in all groups.

The **study design** overview is presented in Figure 1.

Figure 1/ Study design overview



BS = blood sample
M = Month
preVacc = pre-vaccination
postVacc1 = post-MenACWY-TT or *Boostrix* vaccination
postVacc2 = post-*Cervarix* vaccination

Vaccination schedules:

– ACWY-TT group: At Month 0, injection of MenACWY-TT; at Month 1, 2 and 7 IM injection of Cervarix.

– ACWYHPV group: At Month 0, injection of MenACWY-TT and Cervarix; at Month 1 and 6 injection of Cervarix.

– HPV group: At Month 0, 1 and 6 injection of Cervarix.

– Co-ad group: At Month 0, injection of MenACWY-TT, Boostrix and Cervarix; at Month 1 and 6 injection of Cervarix.

– Tdap group: At Month 0, injection of Boostrix and Cervarix; at Month 1 and 6 injection of Cervarix.

Immunological correlates of protection

Bactericidal Assay using rabbit complement rSBA:

Bactericidal antibodies are recognised as surrogate markers of protection. An rSBA cutoff of 8 (reciprocal dilution) has shown to be the most consistent with observed efficacy at four weeks post-vaccination with a meningococcal serogroup C conjugate vaccine in post-licensure efficacy

estimates in the United Kingdom [Andrews, 2003]. The threshold for protection for other serogroups is still to be defined, although it is common practice to extend the cut-off of 8 to rSBA-MenA, rSBA-MenW-135 and rSBA-MenY [CDC, 2006].

Vaccine response for rSBA was defined as post-vaccination titre ≥1:32 one month after vaccination in subjects initially seronegative (rSBA titre <1:8) and at least four times the pre-vaccination antibody titres in subjects initially seropositive (rSBA titre ≥1:8).

Anti-HPV

There are currently no correlates of protection defined for the HPV16 and HPV18 antigens used as part of the Cervarix vaccine. The percentage of subjects with anti- HPV16 titres ≥19 EL.U/mL and anti-HPV18 titres ≥18 EL.U/mL is reported, along with GMTs.

Anti-D and anti-T

Neutralising antibody levels ≥ 0.1 IU/mL are considered to provide protection to diphtheria and tetanus [Plotkin, 2001].

Anti-PT, anti-FHA and anti-PRN

There are no correlates of protection for anti-PT, anti-FHA and anti-PRN antibody. The percentage of subjects seropositive for each antigen (% with antibody concentration equal or above the assay cut-offs), GMCs and pertussis booster responses is reported.

Booster response to PT, FHA and PRN was defined as:

- For subjects with pre-vaccination antibody concentration below the assay cutoffs, post-vaccination antibody concentration ≥ four times the assay cut-offs,

- For subjects with pre-vaccination antibody concentration between the assay cutoffs and below four times the assay cut-offs, post-vaccination antibody concentration ≥ four times the pre-vaccination antibody concentration,

- For subjects with pre-vaccination antibody concentration ≥ four times the assay cut-offs, post-vaccination antibody concentration ≥ two times the pre-vaccination antibody concentration.

Seroconversion was defined as the appearance of antibodies (i.e. titre/concentration ≥ the cut-off value) in the serum of subjects who were seronegative before vaccination.

Study population results

Study population results:

Table 1 Study population (Total Vaccinated cohort)

Number of subjects	ACWY-TT	ACWYHPV	HPV	Co-ad	Tdap	Total
Planned, N	260	260	260	260	260	1300
Randomised, N (Total Vaccinated Cohort)	259	259	261	260	261	1300
Completed, n (%)	256 (98.8)	254 (98.1)	255 (97.7)	254 (97.7)	255 (97.7)	1274 (98.0)
Demographics	ACWY-TT	ACWYHPV	HPV	Co-ad	Tdap	Total
N (Total Vaccinated Cohort)	**259**	**259**	**261**	**260**	**261**	**1300**
Females:Males	259:0	259:0	261:0	260:0	261:0	1300:0
Mean Age, years (SD)	16.3 (4.6)	16.6 (4.4)	16.6 (4.6)	16.6 (4.6)	16.6 (4.5)	16.5 (4.5)
Median Age, years (minimum, maximum)	15 (9, 25)	15 (9, 25)	16 (9, 25)	16 (9, 25)	16 (9, 25)	16 (9, 25)
White - Caucasian / European Heritage, n (%)	87 (33.6)	86 (33.2)	87 (33.3)	87 (33.5)	88 (33.7)	435 (33.5)
Other*, n (%)	86 (33.2)	87 (33.6)	88 (33.7)	86 (33.1)	87 (33.3)	434 (33.4)
Asian - South East Asian Heritage, n (%)	86 (33.2)	86 (33.2)	86 (33.0)	86 (33.1)	86 (33.0)	430 (33.1)

ACWY-TT = Subjects who received MenACWY-TT at Month 0 and *Cervarix* at Month 1, 2 and 7
ACWYHPV = Subjects who received MenACWY-TT and *Cervarix* at Month 0 and *Cervarix* at Month 1 and 6
HPV = Subjects who received *Cervarix* at Month 0, 1 and 6
Co-ad = Subjects who received MenACWY-TT, *Cervarix* and *Boostrix* at Month 0 and *Cervarix* at Month 1 and 6
Tdap = Subjects who received *Boostrix* and *Cervarix* at Month 0 and *Cervarix* at Month 1 and 6
*Other includes all subjects from Dominican Republic who had a mixed heritage.

CHMP comment

The mean age is 15-16 yoa in this study. The recommended age regarding the target population for Cervarix is between 9 and 14 yoa.

IMMUNOGENICITY RESULTS

Confirmatory co-primary objectives

- Non-inferiority of MenACWY-TT co-administered with Cervarix compared to MenACWY-TT alone with respect to rSBA GMTs for serogroups A, C, W-135 and Y one month after vaccination was demonstrated as the UL of the two-sided standardised asymptotic 95% CI for rSBA GMTs ratios (ACWY-TT group/ACWYHPV group) was 1.21, 1.06, 1.07 and 1.12 for serogroups A, C W-135 and Y respectively, which is < the pre-defined limit of 2 for each serogroup.
- Non-inferiority of Cervarix co-administered with MenACWY-TT compared to Cervarix administered alone in terms of HPV16 and HPV18 GMTs as measured by ELISA one month after the third dose of Cervarix was demonstrated as the UL of the two-sided standardised asymptotic 95% CI on the group GMT ratio (HPV group/ACWYHPV group) was 1.15 and 1.29 for HPV16 and HPV18 respectively, which is < the pre-defined limit of 2 for each HPV antigen.
- Non-inferiority of MenACWY-TT co-administered with Cervarix and Boostrix compared to MenACWY-TT alone with respect to rSBA GMTs for serogroups A, C, W-135 and Y one month after vaccination was demonstrated as the UL of the twosided standardised asymptotic 95% CI for rSBA GMTs ratios (ACWY-TT group/Coad group) was 1.43, 1.51, 1.64 and 1.24 for serogroups A, C, W-135 and Y respectively, which is < the pre-defined limit of 2 for each serogroup.

- Non-inferiority of Cervarix co-administered with MenACWY-TT and Boostrix compared to Cervarix co-administered with Boostrix in terms of HPV16 and HPV18 GMTs as measured by ELISA one month after the third dose of Cervarix was demonstrated as the UL of the two-sided standardised asymptotic 95% CI on the group GMT ratio (Tdap group/Co-ad group) was 1.43 and 1.41 for HPV16 and HPV18 respectively, which is < the pre-defined limit of 2 for each HPV antigen.
- Non-inferiority of Boostrix co-administered with MenACWY-TT and Cervarix compared to Boostrix co-administered with Cervarix in terms of anti-D and anti-T antibody concentrations one month after vaccination was demonstrated as the LL of the two-sided standardised asymptotic 95% CI for the group difference (Co-ad group minus Tdap group) in the percentage of subjects with anti-D and anti-T antibody concentrations ≥1.0 IU/mL was -6.90 and -2.23 for anti-D and anti-T respectively, which is ≥ the pre-defined limit of -10%.
- Non-inferiority of Boostrix co-administered with MenACWY-TT and Cervarix compared to Boostrix co-administered with Cervarix with respect to GMC to each discrete pertussis antigen (PT, FHA and PRN) one month after vaccination was not demonstrated as the UL of the two-sided 95% CI for the group ratio of GMC (Tdap group / Co-ad group) for each pertussis antigen was 1.61, 1.93 and 1.87 for PT, FHA and PRN respectively, which is > the pre-defined limit of 1.5.

Table 37 **Confirmatory objective - Non-inferiority of the Co-ad group versus the Tdap group in terms of GMCs for anti-PT, anti-FHA and anti-PRN concentrations, one month after the *Boostrix* vaccination (ATP cohort for immunogenicity)**

					Adjusted GMC ratio (Tdap / Co-ad)*		
	Tdap		Co-ad			95% CI	
Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
anti-PT	254	73.3	245	52.9	1.39	1.20	1.60
anti-FHA	256	466.5	247	282.3	1.65	1.42	1.93
anti-PRN	256	309.2	246	199.5	1.55	1.26	1.90

Co-ad = Subjects who received MenACWY-TT, *Cervarix* and *Boostrix* at Month 0 and *Cervarix* at Month 1 and 6
Tdap = Subjects who received *Boostrix* and *Cervarix* at Month 0 and *Cervarix* at Month 1 and 6
Adjusted GMC = geometric mean antibody concentration adjusted for age strata, country, baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANCOVA model: adjustment for age strata, country and baseline titre - pooled variance)/ LL = lower limit, UL = upper limit)
*The non-inferiority criteria: For anti-PT, anti-FHA and anti-PRN, the UL of the two-sided standardised asymptotic 95% confidence interval (CI) for the group ratio of GMCs (Tdap group/Co-ad group) is ≤ the pre-defined limit of 1.5
Bold text indicates that this value met the statistical non-inferiority criterion

Secondary objectives:

Immunogenicity with respect to components of MenACWY-TT vaccine at one month after vaccination

- Vaccine response against all meningococcal serogroups was observed in a range from 90.2% for rSBA-MenA in the Co-ad group to 100% for rSBA-MenA and rSBA-MenW-135 in the ACWYHPV group across the ACWY-TT, ACWYHPV and Co-ad groups.
- The percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 or rSBA-MenY titres ≥ 1:8 was at least 97.3% for all serogroups across the ACWY-TT, ACWYHPV and Co-ad groups.
- Across the study groups rSBA GMT value ranged from 4649.6 to 5517.1 for rSBAMenA and from 3598.6 to 5091.0 for rSBA-MenC. Consistently in all groups higher GMTs were observed for rSBA-MenW-135 (range from 11663.6 to 18068.3) and rSBA-MenY (range from 11201.2 to 12758.9).

- All subjects in the ACWY-TT group had seroprotective levels of anti-T antbodies (≥ 0.1 IU/mL) with a GMT of 25.4.

Immunogenicity with respect to components of the co-administered Boostrix vaccine at one month after Boostrix vaccination

- Diphtheria and tetanus antigens

- Seroprotective anti-D antibody concentration (≥ 0.1 IU/mL) was observed in all subjects in Co-ad and Tdap groups. GMC values ranged between 4.7 (Co-ad group) and 6.6 (Tdap group) in both groups.

- Seroprotective anti-T antibody concentration (≥ 0.1 IU/mL) was observed in all subjects across the Co-ad and Tdap groups. The GMC values ranged between 15.4 (Tdap group) and 25.9 (Co-ad group) in both study groups.

- Pertussis antigens

- Booster response to PT ranged from 89.0% (Co-ad group) to 92.5% (Tdap group), booster response to FHA ranged from 96.5% (Tdap group) to 97.2% (Co-ad group) and booster response to PRN ranged from 93.9% (Co-ad group) to 96.9% (Tdap group).

- The percentage of subjects with anti-PT, anti-FHA, or anti-PRN concentration ≥ the assay cut-offs was at least 98.0% for all pertussis antigens in the Co-ad and Tdap groups.

- Anti-PT GMC values ranged from 52.9 (Co-ad group) to 73.2 (Tdap group), anti- FHA GMC values ranged from 278.7 (Co-ad group) to 472.4 (Tdap group) and anti- PRN GMC values ranged from 193.4 (Co-ad group) to 318.6 (Tdap group).

Immunogenicity with respect to components of the co-administered Cervarix vaccine at one month after the third dose of Cervarix vaccination.

- The percentage of subjects with anti-HPV-16 concentration ≥ 19 EU/mL and anti- HPV-18 concentration ≥ 18 EU/mL was at least 99.6% across all study groups.

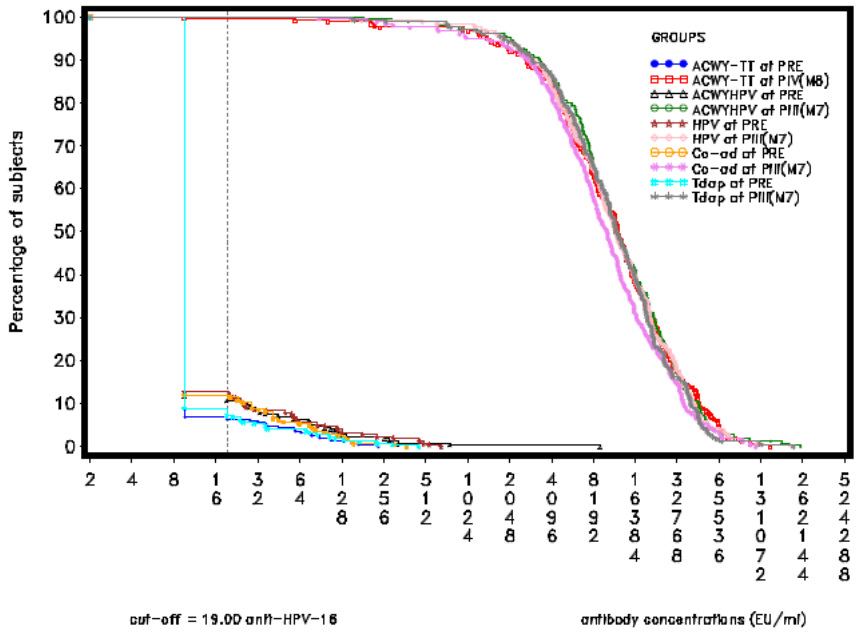
- Anti-HPV-16 GMT values ranged from 9563.8 (Co-ad) to 12124.9 (ACWYHPV) and anti-HPV-18 GMT values ranged from 4306.2 (Co-ad) to 5655.0 (HPV) across all study groups.

Exploratory objectives

The exploratory objectives were related to the comparability of the study vaccine versus the control vaccines in terms of immune response to the different vaccine antigens one month after the vaccination with MenACWY-TT and one month after the third dose Cervarix vaccination.

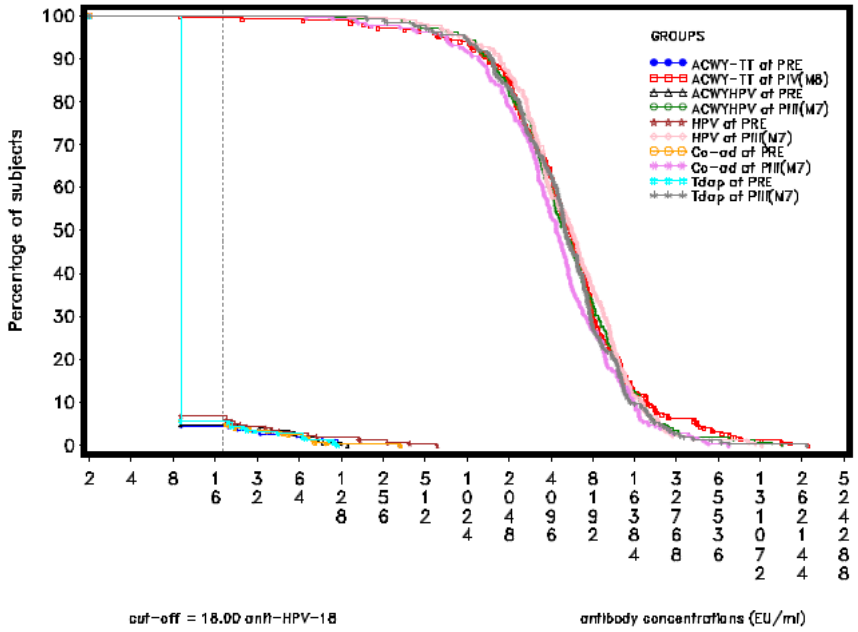
These group comparisons are exploratory and any potential differences should be interpreted with caution considering that there was no adjustment for multiplicity of comparisons and that the clinical relevance of any differences remains unknown.

Figure 7.5 **Reverse cumulative distribution curves for anti-HPV-16 antibody titres, before and one month after the third dose of the Cervarix vaccination (ATP cohort for immunogenicity after Cervarix vaccination)**



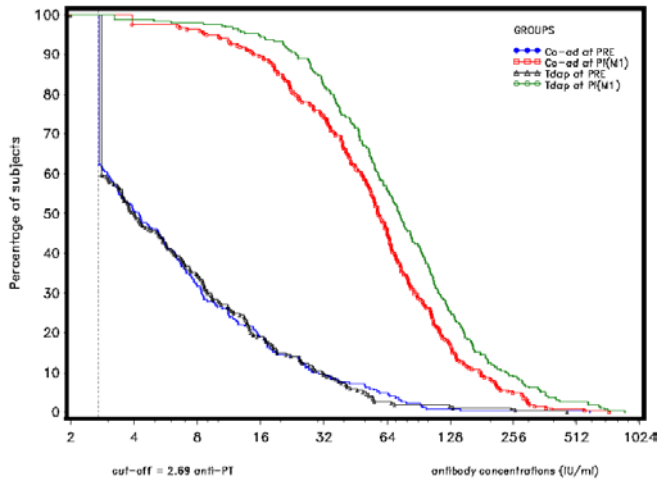
ACWY-TT = Subjects who received MenACWY-TT at Month 0 and Cervarix at Month 1, 2 and 7
ACWYHPV = Subjects who received MenACWY-TT and Cervarix at Month 0 and Cervarix at Month 1 and 6
HPV = Subjects who received Cervarix at Month 0, 1 and 6
Co-ad = Subjects who received MenACWY-TT, Cervarix and Boostrix at Month 0 and Cervarix at Month 1 and 6
Tdap = Subjects who received Boostrix and Cervarix at Month 0 and Cervarix at Month 1 and 6

Figure 7.6 **Reverse cumulative distribution curves for anti-HPV-18 antibody titres, before and one month after the third dose of the Cervarix vaccination (ATP cohort for immunogenicity after Cervarix vaccination)**



ACWY-TT = Subjects who received MenACWY-TT at Month 0 and Cervarix at Month 1, 2 and 7
ACWYHPV = Subjects who received MenACWY-TT and Cervarix at Month 0 and Cervarix at Month 1 and 6
HPV = Subjects who received Cervarix at Month 0, 1 and 6
Co-ad = Subjects who received MenACWY-TT, Cervarix and Boostrix at Month 0 and Cervarix at Month 1 and 6
Tdap = Subjects who received Boostrix and Cervarix at Month 0 and Cervarix at Month 1 and 6

Figure 7.7 **Reverse cumulative distribution curves for anti-PT antibody concentration, before and one month after the Boostrix vaccination (ATP cohort for immunogenicity)**



Co-ad = Subjects who received MenACWY-TT, Cervarix and Boostrix at Month 0 and Cervarix at Month 1 and 6
Tdap = Subjects who received Boostrix and Cervarix at Month 0 and Cervarix at Month 1 and 6

Figure 7.8 **Reverse cumulative distribution curves for anti-FHA antibody concentration, before and one month after the Boostrix vaccination (ATP cohort for immunogenicity)**

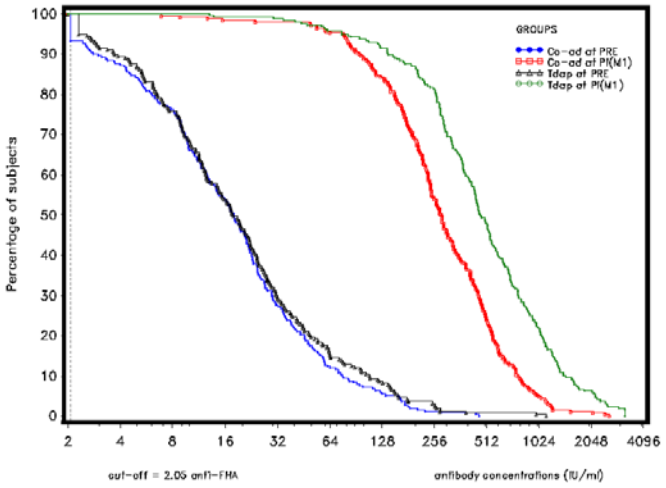


Figure 7.9 **Reverse cumulative distribution curves for anti-PRN antibody concentration, before and one month after the Boostrix vaccination (ATP cohort for immunogenicity)**

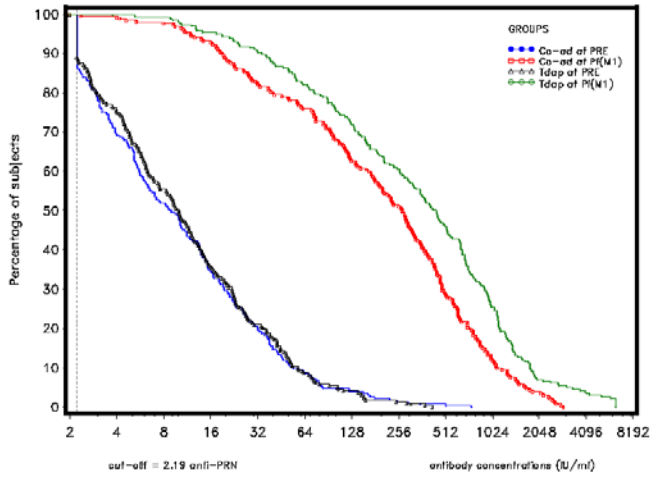


Table 7.15 **Exploratory comparison of the Co-ad group versus the Tdap group in terms of the percentage of subjects with anti-PT, anti-FHA or anti-PRN concentrations above the assay cut-off and above 5 IU/ml, one month after the Boostrix vaccination (ATP cohort for immunogenicity)**

								Difference in percentage (Co-ad minus Tdap)		
		Co-ad			Tdap				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
anti-FHA antibody (assay cut-off=2.046 IU/ml)	9999 IU/ml	247	247	100	256	256	100	0.00	-1.53	1.48
	5 IU/ml	247	247	100	256	256	100	0.00	-1.53	1.48
anti-PRN antibody (assay cut-off=2.187 IU/ml)	9999 IU/ml	246	246	100	256	256	100	0.00	-1.54	1.48
	5 IU/ml	246	242	98.4	256	255	99.6	-1.24	-3.76	0.71
anti-PT antibody (assay cut-off=2.693 IU/ml)	9999 IU/ml	245	240	98.0	254	252	99.2	-1.25	-4.00	1.03
	5 IU/ml	245	239	97.6	254	251	98.8	-1.27	-4.20	1.28

Table 7.16 **Exploratory comparison of the Co-ad group versus the Tdap group in terms of the percentage of subjects with booster response to anti-PT, anti-FHA or anti-PRN concentrations one month after Boostrix vaccination (ATP cohort for immunogenicity)**

								Difference in booster response response rate (Co-ad minus Tdap)		
		Co-ad			Tdap				95% CI	
Antibody	Pre-vaccination status	N	n	%	N	N	%	%	LL	UL
anti-PT	S-	132	96	72.7	138	124	89.9	-17.13	-	-
	S+ (<20 IU/ml)	77	67	87.0	78	72	92.3	-5.29	-	-
	S+ (≥20 IU/ml)	36	28	77.8	38	29	76.3	1.46	-	-
	Total	245	191	78.0	254	225	88.6	-10.62	-17.24	-4.13
anti-FHA	S-	40	37	92.5	34	32	94.1	-1.62	-	-
	S+ (<20 IU/ml)	96	95	99.0	102	102	100	-1.04	-	-
	S+ (≥20 IU/ml)	111	105	94.6	120	111	92.5	2.09	-	-
	Total	247	237	96.0	256	245	95.7	0.25	-3.51	3.99
anti-PRN	S-	85	63	74.1	82	67	81.7	-7.59	-	-
	S+ (<20 IU/ml)	87	78	89.7	92	91	98.9	-9.26	-	-
	S+ (≥20 IU/ml)	74	71	95.9	82	77	93.9	2.04	-	-
	Total	246	212	86.2	256	235	91.8	-5.62	-11.29	-0.15

Table 7.17 **Exploratory comparison of the Co-ad group versus the Tdap group in terms of the percentage of subjects with assay specific booster response to anti-PT, anti-FHA or anti-PRN concentrations one month after Boostrix vaccination (ATP cohort for immunogenicity)**

								Difference in booster response response rate (Co-ad minus Tdap)		
		Co-ad			Tdap				95% CI	
Antibody	Pre-vaccination status	N	n	%	N	n	%	%	LL	UL
anti-PT (IU/ml) (assay cut-off=2.693 IU/ml)	S-	93	80	86.0	101	97	96.0	10.02	-	-
	S+ (<4*cut_off)	89	84	94.4	84	78	92.9	-1.52	-	-
	S+ (≥4*cut_off)	63	54	85.7	69	60	87.0	1.24	-	-
	Total	245	218	89.0	254	235	92.5	3.54	-1.58	8.85
anti-FHA (IU/ml) (assay cut-off=2.693 IU/ml)	S-	16	15	93.8	12	12	100	6.25	-	-
	S+ (<4*cut_off)	46	46	100	50	50	100	0.00	-	-
	S+ (≥4*cut_off)	185	179	96.8	194	185	95.4	-1.40	-	-
	Total	247	240	97.2	256	247	96.5	-0.68	-4.07	2.65
anti-PRN (IU/ml) (assay cut-off=2.187 IU/ml)	S-	32	27	84.4	27	27	100	15.63	-	-
	S+ (<4*cut_off)	90	85	94.4	90	87	96.7	2.22	-	-
	S+ (≥4*cut_off)	124	119	96.0	139	134	96.4	0.44	-	-
	Total	246	231	93.9	256	248	96.9	2.97	-0.74	7.05

Co-ad = Subjects who received MenACWY-TT, Cervarix and Boostrix at Month 0 and Cervarix at Month 1 and 6
Tdap = Subjects who received Boostrix and Cervarix at Month 0 and Cervarix at Month 1 and 6
S- = seronegative subjects (antibody concentration < 2.046 IU/ml for anti-FHA antibody, concentration < 2.187 IU/ml for anti-PRN antibody, concentration < 2.693 IU/ml for anti-PT antibody) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 2.046 IU/ml for anti-FHA antibody, concentration ≥ 2.187 IU/ml for anti-PRN antibody, concentration ≥ 2.693 IU/ml for anti-PT antibody) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Booster response defined as :
For initially seronegative subjects, antibody concentration ≥ 4*cut_off IU/ml at PI(M1)
For initially seropositive subjects with pre-vaccination antibody concentration < 4*cut_off IU/ml : antibody concentration at PI(M1) ≥ 4 fold the pre-vaccination antibody concentration
For initially seropositive subjects with pre-vaccination antibody concentration ≥ 4*cut_off IU/ml : antibody concentration at PI(M1) ≥ 2 fold the pre-vaccination antibody concentration

To summarize according to the MAH, non-inferiority of the immunogenicity (primary analysis) of Boostrix co-administered with MenACWYTT and Cervarix (Co-ad group) was not demonstrated as compared to Boostrix co-administered with Cervarix (Tdap group) with respect to GMC to each discrete pertussis antigen (PT, FHA and PRN) one month after Boostrix vaccination.

Despite failure to meet the non-inferiority criterion, vaccine response rate and GMC fold increase (secondary analysis) between pre- and post-vaccination showed robust booster responses to vaccination for each pertussis antigen in both groups (Co-ad group and Tdap group), suggesting that the statistically significant differences are not deemed to be clinically relevant.

CHMP comment

All the co-primary objectives were met except one.

Non-inferiority of Cervarix co-administered with MenACWY-TT compared to Cervarix administered alone in terms of HPV16 and HPV18 GMTs as measured by ELISA one month after the third dose of Cervarix was demonstrated as the UL of the two-sided standardised asymptotic 95% CI on the group GMT ratio (HPV group/ACWYHPV group) was 1.19 and 1.31 for HPV16 and HPV18 respectively, which is < the pre-defined limit of 2 for each HPV antigen.

In the primary analysis, non-inferiority of the immunogenicity of Boostrix co-administered with MenACWYTT and Cervarix (Co-ad group) was not demonstrated as compared to Boostrix co-administered with Cervarix (Tdap group) with respect to GMC to each discrete pertussis antigen (PT, FHA and PRN) one month after Boostrix vaccination. The co-administration of Tdap Boostrix with Nimenrix and Cervarix one month later tended to elicit lower anti-PT, anti-FHA and anti-PRN GMCs as compared to Boostrix co-administered with Cervarix alone. The clinical relevance of this observation is not known.

Meanwhile in the secondary analysis, the response rates and GMC fold increase between pre- and post-vaccination showed robust responses to vaccination for each pertussis antigen in both groups (Co-ad group and Tdap group), suggesting – according to the MAH - that the statistically significant differences are not deemed to be clinically relevant.

The SmPC should address these results and uncertainty.

The section 4.5 should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies of the vaccines studied. Specifically, the existence or not of clinically relevant interference in the antibody response when co-administration occurs should be adequately addressed.

The current SmPC of Cervarix does not include any information on the co-administration of Cervarix with meningococcal vaccine. Meanwhile, information on the co-administration of Cervarix with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV) - with no clinically relevant interference with antibody response to any of the components of either vaccine – is included in section 4.5 of SmPC of Cervarix. Also, other co-administrations with Cervarix are addressed (combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine or with hepatitis B (rDNA) vaccine).

Meanwhile, the MAH does not consider an update of the SmPC with co-administration of Cervarix with meningococcal vaccine as relevant because of the limited number of European countries having a recommendation for quadrivalent meningococcal vaccination in adolescents.

This rationale cannot be endorsed by the Rapporteur.

This study provides new data regarding co-administration of Cervarix, i e with Nimenrix and with Nimenrix+Boostrix, which warrants an update of its SmPC. Therefore, the MAH is requested to address the results of this study MenACWY-TT-054 especially since non-inferiority of Boostrix co-administered with MenACWY-TT and Cervarix compared to Boostrix co-administered with Cervarix with respect to Geometric mean concentration (GMC) to each discrete pertussis antigen (pertussis toxoid [PT], filamentous hemagglutinin [FHA] and pertactin [PRN]) one month after Boostrix vaccination was not demonstrated although the clinical relevance is unknown. **Issue remains.**

SAFETY RESULTS

The primary analysis was performed on the TVC. As the percentage of vaccinated subjects eliminated from the ATP cohort for analysis of safety was < 5%, an analysis on the ATP cohort for safety was not performed to supplement the TVC analysis.

Solicited adverse events:

During the 7-day (Days 0-6) follow-up period, pain was the most frequently reported solicited local AE at the MenACWY-TT injection site, reported by 58.7%, 54.5% and 60.0% of subjects in the ACWY-TT group, ACWYHPV and Co-ad groups, respectively. Grade 3 local AEs were reported by no more than 2.7% of subjects in all three groups.

During the 7-day (Days 0-6) follow-up period, pain was the most frequently reported solicited local AE at Boostrix injection site, reported by 72.7% and 76.6% of subjects in the Co-ad and Tdap groups, respectively. Grade 3 local AEs were reported by no more than 8.1% of subjects in both groups.

During the 7-day (Days 0-6) follow-up period, pain was the most frequently reported solicited local AE at the injection site after the first dose of Cervarix, reported by 74.8%, 82.9%, 79.2%, 83.5% and 84.7% of subjects in the ACWY-TT, ACWYHPV, HPV, Co-ad and in groups. Grade 3 local AEs were reported by no more than 8.8% of subjects in all study groups.

During the 7-day (Days 0-6) follow-up period, fatigue, headache and myalgia were the most frequently reported general AE across all study groups. - Fatigue was reported by 40.5%, 36.7%, 32.6%, 42.3% and 38.7% of subjects in the ACWY-TT, ACWYHPV, HPV, Co-ad and Tdap groups, respectively. - Headache was reported by 39.0%, 36.3%, 29.9%, 38.1% and 36.4% of subjects in the ACWYTT, ACWYHPV, HPV, Co-ad and Tdap groups, respectively. - Myalgia was reported by 36.7%, 32.0%, 32.6%, 36.9% and 38.7% of subjects in the ACWY-TT, ACWYHPV, HPV, Co-ad and Tdap groups, respectively.

Unsolicited AEs

Unsolicited symptoms were reported by a maximum of 16.2% of subjects across the study groups and unsolicited symptoms assessed by the investigator as causally related to vaccination were reported by no more than 5.0% of subjects across the study groups. Grade 3 unsolicited symptoms were reported by a maximum of 1.9% subjects across the study groups and grade 3 unsolicited symptoms assessed by the investigator as causally related to vaccination was reported by no more than one subject in the Tdap group only.

During the 31-day post-Dose 1 vaccination period: - At least one unsolicited symptom was reported by 14.3%, 13.5%, 13.4%, 16.2% and 14.9% of subjects in ACWY-TT, ACWYHPV, HPV, Co-ad and Tdap groups, respectively. - Grade 3 unsolicited symptoms were reported by 1.2%, 1.2%, 1.9%, 1.5% and 1.9% of subjects in ACWY-TT, ACWYHPV, HPV, Co-ad and Tdap groups, respectively. - Unsolicited symptoms assessed as causally related to vaccination by the investigator were reported by 2.3%, 3.1%, 1.1%, 5.0% and 1.5% of subjects in ACWY-TT, ACWYHPV, HPV, Co-ad and Tdap groups, respectively. - Grade 3 unsolicited symptoms assessed as causally related to vaccination by the investigator were reported by 0.4% of subjects in the Tdap group only.

During the 31-day post-Dose 2 vaccination period for ACWY-TT group: - At least one unsolicited symptom was reported by 8.5% of subject after the first dose of Cervarix. - Grade 3 unsolicited symptoms were reported by 1.2% of subject after the first dose Cervarix. - Unsolicited symptoms assessed as causally related to vaccination by the investigator were reported by 0.4% of subject after the first dose Cervarix.

Serious adverse events:

SAEs were reported by a maximum of 22 subjects across study groups of which all recovered and the SAEs had resolved by study end. Among the child cases, three SAEs were reported for one infant in the Tdap group with fatal outcome. None of the SAEs (fatal and non-fatal SAEs) were considered by the investigator as causally related to vaccination.

- During the entire study period in the overall vaccinated population, at least one SAE was reported by three subjects (1.2%) in the ACWY-TT group, two subjects (0.8%) in the ACWYHPV group, five subjects (1.9%) in the HPV group, seven subjects (2.7%) in the Co-ad group and six subjects (2.3% [includes one child case]) in the Tdap group.
- During the entire study period in the child population, three SAEs were reported for one infant (0.4%) in the Tdap group.
- None of these SAEs were considered by the investigator as causally related to vaccination

Fatal events:

Three SAEs (prematurity, low weight at birth and respiratory distress syndorme) were reported for the offspring of a 25-year female subject. The subject had received one dose of Boostrix and two doses of Cervarix before conception. Nine months after the second dose of Cervarix vaccination and 10 months after Boostrix vaccination the baby was born prematurely by normal vaginal delivery at 34 weeks of gestation. He died after 13 days and his death and none of the SAEs were considered by the investigator as causally related to Boostrix and/or Cervarix vaccination.

Non-fatal events:

Twenty-two non-fatal SAEs were reported across the five groups during the entire study period. These SAEs were all recovered/resolved by the study end and none of them were considered by the investigator as causally related to the vaccination.

Adverse events leading to premature discontinuation of study vaccine and/or study:

No AEs leading to premature discontinuation of study vaccine and/or study were reported during the study period.

Other significant adverse events:

From first dose up to study end, at least one NOCI was reported by no more than 1.2% of subjects and no pIMDs were reported by any subjects across all study groups.

Pregnancy

During the entire study period, 21 pregnancies were reported across the five groups (two in the ACWY-TT group, five in the ACWYHPV group, four in the HPV group, six in the Co-ad group and four in the Tdap group). All 21 subjects had been exposed to study vaccines before conception (at Visit1) and were discontinued from further treatment, except for one subject who received the second dose of Cervarix in the first trimester of pregnancy at Visit 2 as the pregnancy test was negative. The pregnancy outcomes are as follows:

- One subject had an elective termination with no apparent congenital anomaly
- 13 subjects had a live infant with no apparent congenital anomaly
- Two subjects had spontaneous abortion with no apparent congenital anomaly (according to study protocol a pregnancy outcome with spontaneous abortion is considered an SAE).
- Three subjects were still pregnant at the end of the study
- Two subjects were lost to follow-up .

Safety summary

No safety concerns were identified. Nimenrix, Boostrix and Cervarix vaccines were well tolerated when coadministered to 9-25 years old females, and their safety profiles were not affected by coadministration of the three vaccines.

CHMP comment

No concerns were identified. Nimenrix, Boostrix and Cervarix vaccines were well tolerated when coadministered to 9-25 years old females. Their safety profiles were not affected by co-administration of the three vaccines.

3. Rapporteur's overall conclusion

Based on the epidemiology of disease caused by N. meningitidis and Bordetella pertussis, adolescents stand to benefit from vaccination against both pathogens. Co-administration of MenACWY-TT Nimenrix with Boostrix (Tdap) was evaluated in male and female subjects aged between 11 and 25 years (adolescents and adults) in a separate clinical study. The current study MenACWY-TT-054 evaluated an unprecedented co-administration of Nimenrix , Cervarix and Boostrix as compared to administration of Nimenrix and Cervarix vaccines alone in females from 9 to 25 years of age. The current SmPC of Cervarix does not include any information on the co-administration of Cervarix with meningococcal vaccine. Co-administration of the three vaccines may contribute to improve the implementation and coverage of adolescent vaccination programmes.

This phase III study was meant to assess the immunogenicity and reactogenicity of Nimenrix administered alone as compared to Nimenrix co-administered with Cervarix or co-administered with Cervarix and Tdap Boostrix in female adolescents and young adults at 9-25 years of age.

All the co-primary objectives were met except one. In the primary analysis, non-inferiority of Cervarix co-administered with MenACWY-TT compared to Cervarix administered alone in terms of HPV16 and HPV18 GMTs as measured by ELISA one month after the third dose of Cervarix was demonstrated.

Also, non-inferiority of Cervarix co-administered with Nimenrix and Boostrix compared to Cervarix co-administered with Boostrix was demonstrated.

Non-inferiority of the immunogenicity of Boostrix co-administered with Nimenrix and Cervarix (Co-ad group) was not demonstrated as compared to Boostrix co-administered with Cervarix (Tdap group) with respect to GMC to each discrete pertussis antigen (PT, FHA and PRN) one month after Boostrix vaccination. The co-administration of Tdap Boostrix with Nimenrix and Cervarix one month later tended to elicit lower anti-PT, anti-FHA and anti-PRN GMCs as compared to Boostrix co-administered with Cervarix alone. The clinical relevance of this observation is not known.

As in the secondary analysis, the response rates and GMC fold increase between pre- and post-vaccination showed robust responses to vaccination for each pertussis antigen in both groups (Co-ad group and Tdap group), suggesting – according to the MAH - that the statistically significant differences are not deemed to be clinically relevant.

According to the Rapporteur, the SmPC of Cervarix should address these results and uncertainty. Indeed, the section 4.5 should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies of the vaccines studied. Specifically, the existence or not of clinically relevant interference in the antibody response when co-administration occurs should be adequately addressed.

The current SmPC of Cervarix does not include any information on the co-administration of Cervarix with meningococcal vaccine. Meanwhile, information on the co-administartion of Cervarix with a Boostrix or Boostrix polio - with no clinically relevant interference with antibody response to any of the components of either vaccine – is included in section 4.5 of SmPC of Cervarix. Also, other co-administration with Cervarix were addressed (combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (Twinrix) or with hepatitis B (rDNA) vaccine) (Engerix B).

However, the MAH does not consider an update of the SmPC with co-administration of Cervarix with meningococcal vaccine as relevant because of the limited use / limited number of European countries having a recommendation for quadrivalent meningococcal vaccination in adolescents.

The rationale of the MAH cannot be supported and endorsed by the Rapporteur. This study provides new data regarding co-administration of Cervarix, i e with Nimenrix and with Nimenrix+Boostrix, which warrants an update of its SmPC. Therefore, **the MAH is requested to address the results of this study MenACWY-TT-054** especially since non-inferiority of Boostrix co-administered with MenACWY-TT and Cervarix compared to Boostrix co-administered with Cervarix with respect to Geometric mean concentration (GMC) to each discrete pertussis antigen (pertussis toxoid [PT], filamentous hemagglutinin [FHA] and pertactin [PRN]) one month after Boostrix vaccination was not demonstrated although the clinical relevance is unknown. The MAH is required to present a type II variation to update section 4.5 of the Cervarix SmPC.

MS comments

It is agreed with the Rapporteur that the SmPC section 4.5 of Cervarix should be updated with the information from this study.

Although the MAH argued that use of quadrivalent meningococcal vaccine in adolescents is limited in EU, this appears to be changing with the upcoming Men W. For example in the Netherlands it has recently been decided to vaccinate in 2018 one year cohort of adolescents with a Men ACWY vaccine. It

is important for prescribers to know that there is no immune interference between the two vaccines observed.

In addition although the clinical relevance of the lower pertussis response (PT,FHA, PRN) with co-administration of all three vaccines is not known, it is recommended to add this information in the SmPC, because the current information mentions that no interference was found by concomitantly administration of Cervarix and dTpa(-IPV) vaccines while sequential administration resulted in lower anti-HPV16 and anti-HPV-18 response.

MAH response to the assessment comments

After internal discussions, the MAH now agrees to update the interaction section of the Cervarix SmPC with these new available co-administration data.

CHMP conclusion

As requested, the commitment in this article 46 procedure P46 093 to update the Cervarix SmPC with the data from study MenACWY-TT-054 in a new type II variation is accepted by the MAH and therefore this PAM is fulfilled.

☒ PAM fulfilled (all commitments fulfilled) - No further action required