PRAC (co)-rapporteur's referral 2nd Updated preliminary assessment report

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Human papillomavirus (HPV) vaccines

Cervarix: EMEA/H/A20/1421/C/0721/0071

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Administrative information

INN (or common name) of the active substance(s)	Cervarix (Bivalent HPV vaccine (types 16, 18))
Pharmaco-therapeutic group (ATC code)	J07BM02
Pharmaceutical form(s) and strength(s)	All approved

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Commercially confidential information

Does this AR contain any information which may potentially be considered CCI*? *(e.g. personal data, unpublished studies, info on manufacturing*	No ☐ Yes ☐ specify type of info and relevant pages:

process, other info highlighted as confidential by the MAHs)	

**Further information on the definition of CCI can be found in EMEA/45422/2006.*

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List of abbreviations

AE	Adverse event
CRPS	Complex Regional Pain Syndrome
DLP	Data Lock point
EMA	European Medicines Agency
HPV	Human papilloma virus
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MSC	Medically significant condition
O/E	Observerd vs Expected
pIMDs	Potentially immune-mediated diseases
POTS	Postural Orthostatic Tachycardia Syndrome
PT	Preferred term
TVC	Total vaccinated cohort

1. Background information

Human papillomavirus (HPV) vaccines have been authorised in Europe for the prevention of premalignant lesions and cervical and various other cancers caused by HPV infection since 2006. Following approval, these vaccines have been introduced in national immunisation programs worldwide, including in most EU member states.

The efficacy and safety of these medicinal products has been clearly demonstrated and the benefit of these vaccines in protecting against HPV related diseases is well established. Since launch, approximately 55 million subjects are estimated to have been vaccinated with Gardasil worldwide. Cumulative marketing exposure to Cervarix is estimated as being around 19 million subjects worldwide.

Routine surveillance of suspected serious adverse drug reaction reports have raised questions on the potential association between the use of the vaccines and two syndromes in particular, which are known as Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS) (1 signal raised in 2013 on POTS and 1 signal raised in 2013 on CRPS). The vast majority of the reported cases do not have a well-defined diagnosis. These syndromes have been reviewed repeatedly by the PRAC within routine safety follow up procedures, and a relationship with vaccination has not been established in these previous procedures.

CRPS symptoms are severe chronic pain which is out-of-proportion to what would be expected, allodynia, hyperesthesia, swelling, changes in the skin temperature and colour of the arms or legs, sweating, movement disturbances (tremor, weakness, dystonia) and trophic changes (abnormal hair and nail growth). POTS is characterised by an abnormally large increase in heart rate when changing from a lying down to a standing up position, without any orthostatic hypotension. In POTS, this excessive heart rate increase may be accompanied by a range of symptoms which may include light headedness, visual blurring, palpitations, tremulousness and weakness (especially of the legs), as well as fatigue, shortness of breath, chest pain, concentration difficulties, and headaches.

Individual case reports and case series of CRPS and POTS have been reported in the literature following HPV vaccination from several geographically distinct locations. Literature reports of CRPS come from Australia, Germany and Japan and reports of POTS originate from USA, Japan and Denmark.

There are uncertainties regarding the underlying pathogenesis for CRPS and POTS and an association between HPV vaccination and CRPS or POTS has also not been established. These conditions have been well known for a long time and before the introduction of the HPV vaccines.

It is recognised that these conditions can occur in the general non-vaccinated population and it is considered important to undertake further review to determine whether the number of cases reported with HPV vaccine is greater than would ordinarily be expected.

2. Referral notification

On 9 July 2015 the EC triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and asked the Agency to give its opinion at the latest by 31 July 2016 on whether there is evidence of a causal association between HPV vaccination and CRPS and/or POTS, if research efforts should be strengthened, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

3. Assessment

3.1. Introduction

Cervarix (Bivalent HPV vaccine (types 16, 18)) is a non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. This vaccine is adjuvanted with AS04 (composed of aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A (MPL)) which has been shown to induce a high and long lasting immune response in clinical trials.

Up to the data lock point (DLP) of this referral (15 June 2015), *Cervarix* is indicated in females from 9 years of age onwards for the prevention of persistent infection, premalignant genital (cervical, vulvar and vaginal) lesions and cervical, vulvar and vaginal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV). Besides, a type II variation (procedure EMEA/H/C/000721/II/0067) is currently under assessment to extend the indication of the Product Information for Cervarix to the prevention of premalignant anal lesion and anal cancer.

The age at which people receive the vaccine, e.g. in the context of a national vaccination programme, can vary between countries depending on their official recommendations. The vaccination schedule depends on the age of the subject:

- From 9 up to and including 14 years: 2 doses each of 0.5 ml. The second dose given between 5 and 13 months after the first dose[*]; or 3 doses each of 0.5 ml at 0, 1, 6 months[†]
- From 15 years and above: 3 doses each of 0.5 ml at 0, 1, 6 months[†]

Although the necessity for a booster dose has not been established, an anamnestic response has been observed after the administration of a challenge dose.

Cervarix is for intramuscular injection in the deltoid region.

Cervarix was first approved on 18 May 2007 in Australia and is currently approved in 135 countries worldwide.

At the data lock point (15 June 2015) used for this analysis, a total of 57 094 396 doses have been distributed worldwide, and the number of subjects exposed to at least one dose of Cervarix can be estimated to be between 19 031 465 and 57 094 396.

3.2. Quality aspects

N/A

3.3. Non-clinical aspects

N/A

3.4. Clinical aspects

3.4.1. Efficacy

N/A

[*] If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered
[†] If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose

3.4.2. Safety

Data on safety

Clinical safety data

For the purpose of the referral, the MAH was requested to provide an in depth review of the CRPS and POTS cases observed within all clinical studies. To respond to this request, the MAH has pooled the safety data from 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups) (DLP of 15 June 2015).

The analysis of available data did not identify any serious or non-serious adverse event of CRPS or POTS, regardless of the search strategy method, i.e. when searching for cases which contain the MedDRA PT 'CRPS' or 'POTS', or when searching for any cases that include signs and symptoms of CRPS (as according to *Harden et al. 2010*), or POTS (as according to *Raj 2013 and Sheldon et al. 2015*).

Post marketing safety data

CRPS

The assessment of the post-marketing data provided by the MAH has shown that:

- out of 49 spontaneous reports of CRPS (i.e. PT CRPS), 5 cases have been considered as confirmed CRPS, i.e. with fulfilment of the Budapest clinical diagnostic criteria for CRPS. In 3 of these cases, a causal relationship with Cervarix vaccination cannot be ruled out, including 1 serious case resolved with sequelae. Among the 44 remaining *potential* CRPS cases (i.e. PT CRPS reported but insufficient information or incomplete fulfilment of the diagnostic criteria), only in 8 cases, including 4 serious cases with an unknown outcome in 50% and recovering/resolving in the other half, the involvement of Cervarix cannot be ruled out;

- besides, 10 cases of *potential* CRPS have been identified by applying the search strategy of signs and symptoms of CRPS (cases not reporting PT CRPS). In 2 cases the involvement of Cervarix administration could not be ruled out, one of which was serious and no recovery was observed;

- the number of CRPS cases following administration of Cervarix is considered low compared to 57 million doses of Cervarix distributed globally. However, the low number might be contributed by the problem of underreporting of ADRs in general, and more specific, the difficulty of diagnosing CRPS being a complex syndrome with a variety of signs and symptoms in highly variable combinations with a variable progression over time. Furthermore, there is no golden standard diagnostic test for CRPS available, remaining CRPS as a syndrome of exclusion of other diseases with similar signs and symptoms, and no overall consensus on the clinical diagnostic criteria of CRPS (*Rockett 2014*). However the most widely accepted diagnostic criteria are the Budapest criteria described by *Harden et al. 2010*. All taken together, many patients could be undiagnosed;

- despite the fact that the Observed vs Expected analysis is based on many assumptions, which cannot be verified, this analysis has suggested that the number of observed CRPS cases is low compared to those expected, except in Japan. Based on reported cases in Japan and UK, a reporting rate at 0.31 cases per 100,000 doses (48/15,668,109) can be estimated. When this rate is applied to the number of doses distributed worldwide, 175 cases would have been reported, assuming that the reporting pattern is similar in other countries.

POTS

The assessment of the post-marketing data provided by the MAH has shown that:

- out of the 19 cases identified with POTS PT and 7 cases identified with combinations of proxy PTs, 2 cases could likely be cases of POTS following HPV vaccination, 4 cases are possibly cases of POTS following HPV vaccination, and the other cases are not POTs, or possible POTS not following vaccination, or unclassifiable cases;

- The O/E analysis suggest that the number of observed POTS cases is low compared to those expected, even in Japan. However, as for CRPS, the O/E methodology used in this analysis is also based on many assumptions, which cannot be verified.

Literature

CRPS

Data from the literature do not point out a causal relationship between HPV vaccination and the onset of CRPS. However this cannot be ruled out for the following reasons:

- the disease is probably caused by a multi-factorial process, including inflammatory and immune related factors (*Bruehl 2015*),
- CRPS occurs most commonly in women between 50 and 70 years of age *(Rockett 2014)* and is relatively rare in childhood and adolescence (*Borchers & Gerschwin 2014*) which is the target population of HPV vaccination,
- paediatric CRPS is mostly triggered by minor trauma (*Borucki & Greco 2015*).

POTS

Few cases of POTS following a vaccination with Cervarix were published and those cases were included in the MAH safety data base and discussed here-above (*Kinoshita et al. 2014*).

An expert group published recently a consensus statement on the definition , physiology, diagnosis, and treatment of POTS (*Sheldon et al. 2015*). The physiology of the condition include peripheral autonomic denervation, heperadrenergism, deconditioning, and anxiety. Beside physical examination and personal and family history, the diagnosis of the patient involve cardiologic investigations, biology (including thyroid, norepinephrine), autonomic neuropathies, modifying factors, potential triggers. A full autonomic system review should assess symptoms of autonomic neuropathy. A tilt-table test may be useful

Demonstrated risks

CRPS

Within the data submitted by the MAH, 3 confirmed and 10 potential cases of CRPS for which the involvement of Cervarix cannot be excluded, have been identified. This is based on a strong temporal relationship between the events and administration of the vaccine, the absence or unknown relevant medical history, and the absence of other events which might explain the symptoms.

POTS

In conclusion, very few cases of POTS following HPV vaccination were identified. From data available, all conditions other than vaccination which could potentially be associated to POTS cannot be systematically excluded. However, a potential association between HPV vaccination and POTS cannot be ruled out

Uncertainty about risks

CRPS

A potential involvement of Cervarix in the occurrence of CRPS has not been demonstrated, but cannot be completely excluded at this stage. Whether the development of CRPS post-vaccination could be due to the injection or the vaccine itself cannot be determined as in literature, CRPS was also reported following venipuncture, intravenous drug administration and other vaccinations (*Richards et al. 2012*; *Kwun et al. 2012*; *Genc et al. 2005*; *Jastaniah et al. 2003; Bilic et al. 2013*). However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections.

It appears that CRPS is caused by a multifactorial process involving both peripheral and central mechanisms. Potential mechanisms include nerve injury, ischemic reperfusion injury or oxidative stress, central sensitization, peripheral sensitization, altered sympathetic nervous system function or sympatho-afferent coupling, inflammatory and immune related factors, brain changes, genetic factors, psychological factors and disuse (*Bruehl 2015*). Little is known how these mechanisms might interact. Given the diversity of presentations seen in CRPS, the relative contributions of different mechanisms probably differ across individual patients and even within patients over time (*Bruehl 2015*). The heterogeneity in the constellations of signs and symptoms in individuals and the great variability in the response to specific treatments suggest the existence of distinct subgroups with different underlying pathophysiological mechanisms (*Borchers & Gerschwin 2014*).

CRPS can occur at any age, but is relatively rare in childhood and adolescence, with paediatric patients constituting <10% of CRPS patients seen at tertiary centres. Onset of paediatric CRPS occurs most frequently in early adolescence (peak age of onset is around 12-13 years of age), with the lower end of the range usually being 7 to 9 years (*Borchers & Gerschwin 2014*; *Borucki & Greco 2015*). CRPS is rarely seen in young children before the age of 6 (*Borucki & Greco 2015*).

Whether paediatric CRPS is a subgroup of the same disorder as in adults or a different entity entirely is still being questioned, because of a potential different presentation of signs and symptoms in children/adolescents compared to adults (*Borchers & Gerschwin 2014*).

POTS

As pointed by Raj et al., POTS is a syndrome, not a disease (*Raj 2013*). Although orthostatic tachycardia is the main sign of the condition, the syndrome can be associated (or not) to a variety of conditions.

When considering the possibility of POTS after HPV vaccination, two conditions are of major interest:

1) POTS as an autoimmune condition: the autoimmune theory which is supported by the identification in a significant proportion of the cases of antibodies, the report of viral infections before onset and the presence of autoimmune markers (*Blitshteyn 2015*).

2) POTS as a dysfunction of the autonomic nervous system: in a recent publication, WHO identified in Vigibase 21 cases of gastrointestinal motility disorders after HPV vaccine (*Chandler 2015*), those conditions being suspected to be caused by autonomic neuropathies. Dysfunctions of the autonomic nervous system may present under various forms. The identification of dysautonomic conditions of interest should be discussed for future surveillance.

The background incidence of POTS in the general population in unknown, but based on our external expert's experience should be low.

The diagnostic criteria of POTS are based on the tilt-test or active standing test. Two studies have suggested that having a positive tilt-test in an adolescent patient – regardless of symptoms – would not be that uncommon (*Singer et al. 2012, Zhao et al. 2015*). However, for a definite diagnosis of POTS other symptoms – such as light-headedness, dizziness, or fatigue – need to be present as well. It is not known how commonly these symptoms occur in the adolescent population in combination with a positive tilt-test, which would be required for a definite diagnosis of POTS

4. Consultation with expert group

A SAG vaccines meeting was convened on 21 October 2015 to provide answers to the list of questions on the above referral adopted by PRAC at their October 2015 plenary meeting. The draft SAG-Vaccines responses were shared on 28 October 2015 (th:

1. What is the current understanding about the pathophysiology of Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS)?

CRPS is defined as continuing pain which is disproportionate to the inciting event, may be associated with dysautonomic signs and symptoms and is usually confined to a single limb. Other symptoms, including psychological symptoms are recognised, particular amongst those with more persistent pain. CRPS typically follows an episode of trauma including fracture of the wrist or carpal tunnel syndrome surgery, or immobilisation of the limb. The experts were not familiar with cases in which needle trauma from an immunisation had triggered an episode of CRPS. Consequently, the onset of symptoms of CRPS are difficult to define because the syndrome is usually only diagnosed from the point when normal recovery from the initiating trauma should have occurred (may as much as 5-7 weeks post-trauma), and is usually only recognised some time later among those with continuing pain afterwards. The majority of CRPS cases (>70%), improve over time and show no recurrence; recovery is higher in children. The pathogenesis of CRPS is incompletely understood but researchers are investigating genetic, inflammatory, auto-immune and psychological contributors to the condition.

Based on the overall considerations made by the CRPS and pain experts who studied the reports of the cases, the SAG concluded that most of the reported cases ascribed to HPV vaccines, including those from Japan, do not clearly fall into the definition of CRPS as it is currently understood using the available diagnostic criteria. In some of the cases the available information is insufficient to make a diagnosis. In many cases the long interval from vaccination, to onset of symptoms reduces the plausibility of an association.

POTS is a systemic syndrome known for a long time under different names and still poorly defined. POTS patients typically show persistent tachycardia for more than 10 minutes upon standing, as well as an increase in heart rate, which in children should be ≥ 40bpm, without hypotension. A diagnosis of POTS cannot solely rely on these symptoms; other symptoms (e.g. syncope, fatigue, headaches etc) vary across patients and are otherwise non-specific. Consequently, POTS seems to be defined only if given this label (i.e. a subjective syndrome), but it is otherwise not particularly well characterised. POTS overlaps with orthostatic tachycardia which occurs as a normal physiological response on standing and may be prolonged following a period of bed rest or inactivity as a result of "deconditioning". It was noted that many of the POTS cases that are part of the referral do not fit well into the typical syndrome definition, or are poorly documented or inadequately diagnosed.

Those with the diagnosis of POTS are typically pubertal high achieving girls who are very active and often athletic, may have had recent illness, although stress, surgery, hypermobility in joints, psychological and genetic predisposition may be involved. Fatigue is a common symptom in POTS patients and features of chronic fatigue syndrome (CFS) may dominate. The deconditioning from bed or chair rest (e.g. following an acute illness), may lead to POTS-like syndrome but can be managed by

rehabilitation, and should be differentiated by other cases of POTS which are persistent and particularly debilitating for individuals.

POTS pathophysiology is still poorly understood, and the lack of strict application of diagnostic criteria hampers study of the syndrome. Researchers are currently investigating autonomic dysfunction, autoimmunity and genetic predisposition to POTS, but there is no clear evidence regarding the underlying cause=.

The SAG were of the view that the vast majority of the cases presented in the literature and database review do not fit with the accepted definitions of POTS or CRPS and would more appropriately be labelled as having features of CFS. It is currently not clear how many of the remaining reported cases are truly POTS and CRPS, but it seems to be a small proportion of those which have been documented so far. The SAG noted that CFS is difficult to formally diagnose from the available reports but the collection of features fit better than with CRPS or POTS in many of them. It was also noted that some of the patients reported from Denmark, likely had CFS and had become deconditioned as a result of fatigue symptoms, such that they also now had features that could lead to the misdiagnosis of POTS The cause of CFS is a topic of intense research activity but the pathophysiology of the condition remains unclear.

The SAG were not aware of any pathophysiological evidence that vaccines in general, or HPV vaccine in particular, leads to CRPS or POTS. Although the association of trauma with CRPS suggests plausibility that the condition might be triggered by a needle, the pain experts did not consider this to be a likely trigger given the lack of cases presenting to the clinics of the assembled experts, despite the large numbers of adolescents receiving immunisations in their countries. The SAG were of the view that the majority of the cases labelled as POTS either didn't fit the accepted definition or seemed to be more likely CFS cases with deconditioning (as a result of fatigue and inactivity), leading to a misdiagnosis of POTS. The SAG noted that CFS is common amongst adolescent girls in developed countries and that the condition is very distressing for the affected individual and their families but usually resolves through adolescence.

2. What is the strength of the available information with respect to the cases of CRPS and POTS which have been reported in girls previously exposed to HPV vaccination?

It was not made explicit by the question whether it should have been interpreted as the strength of the existing information or the strength of the association between the cases of CRPS and POTS and HPV vaccines. The SAG opined to address both elements.

Regarding the strength of the information, the SAG noted the known weakness and limitations of spontaneous passive reporting systems. However, the SAG agreed that spontaneous reporting remains a sensitive tool to pick up unexpected rare signals which are not predicted at the time of introduction of a vaccine. The system was effective in identifying signals which warrant investigation but, because cases might not always be reported, is not as sensitive as active surveillance. A major limitation of the evidence provided is the inadequate reporting of the case definitions in the databases, which may continue to affect future investigations. The SAG noticed that most of the cases presented in the referral could possibly better fit the definition of CFS or at least include some features of chronic fatigue syndrome and less clearly fit the formal definitions of CRPS or POTS.

This observation is important, since a careful study, with better methodology has already been undertaken for CFS. The CPRD study on CFS, one of the most robust studies that were included in the referral, was found to provide robust data demonstrating a lack of an association between HPV vaccines and CFS.

The observed/expected (O/E) analysis conducted by the MAHs in the frame of the referral, and thoroughly assessed by the Rapporteurs, seems to be as robust as it could be, given the difficulties with the type of data gathered and the assumptions made. One of the difficulties mentioned was the background rates estimation; background rates seem to vary across ages and over time possibly due to changes in diagnostic criteria. It was noted that the O/E analyses covered a range of scenarios taking into account uncertainties in both numerator and denominator, and still showed no association of HPV vaccine with POTS or CRPS.

As far as the strength of association between HPV vaccines and POTS and CRPS is concerned, the SAG concluded that an association is not currently supported by the data, although limitations of the data, as mentioned above, must be recognised. Concerning the data that is available from the literature case series, these do not support of an association because of their inherent limitations and bias.

In conclusion, despite the uncertainties due to the limitations of case series and passive reporting, the SAG agreed that there is no evidence of a signal which warrants further investigation. However, the SAG recognised that there is public concern in some countries, which warrants ongoing observation in order to monitor future trends. While the SAG were of the view that there is no association demonstrated, they were aware that additional work to provide further evidence would be helpful but challenging. Even the standard argument of a temporal association between the trigger and the event may be of limited help, in view of the large range of time lag between onset of the conditions and vaccinations. This is an accepted limitation from a pharmacovigilance point of view.

3. a) Based on the available information, are there specific characteristics that should be monitored in post-marketing surveillance?

There was a clear view from the SAG that enhanced surveillance should continue to be performed since POTS and CRPS remain a public concern in a number of countries.

b) If yes, then:

i. What are these characteristics:

CRPS is coded in international used systems, e.g. MedDRA or ICD10 code, and reference could be made to these. The SAG agreed that 'continuous limb pain' or 'general pain' should be used as a non-specific, but possibly sensitive term that could be used to retrieve potential cases of CRPS in safety databases that had not been appropriately labelled as CRPS; although these terms are not specific, using the tight definition of the syndrome might affect the sensitivity of the searches. Flagging search terms prospectively could help in seeking adequate follow-up of potential cases. It is not clear whether these characteristics would change the reporting rates seen, as it should be acknowledged that databases searches cannot provide a robust answer in case of lack of defined diagnostic codes.

Concerning POTS, it is possible to search for symptoms of the syndrome or specific features of the diagnosis of POTS such as the table-tilt test, which may allow identification of data from safety databases, albeit with limited sensitivity. POTS is coded in MedDRA, however due to the lack of awareness, or even consistent clinical /diagnostic views, around this syndrome in many countries, and due to the difficulties with diagnosis this term might be used only seldom. Due to all the uncertainties mentioned, the SAG could not come to a clear conclusion on specific characteristics that could improve case identification in large databases. However, the SAG noted that many POTS cases include features of CFS and that many of the cases labelled as POTS in the review fitted better with a CFS definition such that identification of CFS cases may be valuable in extracting data on POTS.

Considering the possible overlap of CRPS/POTS cases with CFS, which has an established code and a clear set of symptoms, the SAG considered that CFS codes and symptoms could be useful characteristics to be monitored.

ii. Discuss the feasibility of performing further studies with the potential to provide robust and meaningful results within existing data sources in Europe.

The SAG opinion was that enhanced surveillance should continue as main pharmacovigilance measure.

In addition, the SAG considered other measures, e.g. population-based registries; the main issue identified with this approach was the risk of bias and the lack of consistently used diagnostic codes, which may lead to inconclusive results.

Concerning the feasibility of performing studies, overall they might be feasible, despite the challenges due to the large sample size and confounders. However, concern was expressed by the SAG about the risk that studies may lead to results difficult to interpret due to the risk of bias, e.g. media reporting or other confounding. In addition it was stressed that any methods used should be independent of ascertainment of cases as this cannot be readily dealt with by statistical methods. Several experts considered only retrospective cohort studies to be potentially of use, and that these should predate media interest.

Finally, the SAG recommended for PRAC consideration that for example the CPRD study, or similar, could be built upon and updated to cover the more recent period previous to the media reporting, and to specifically include the characteristics for CRPS and to increase the sensitivity of some characteristics of CFS to ensure cases which less closely met the case definition could be identified. Such an update may or may not identify more cases than those already identified so far, due to the overlap in syndromes; however there may be some benefit in looking again at the definitions based on the current reporting, as it may shed some further light on CRPS and POTS in association with HPV vaccines.

In conclusion, as far as feasibility of further studies is concerned, there are some designs which perhaps the PRAC could consider (e.g. CPRD study or similar retrospective designs), being aware of the risk of bias; however, in light of the lack of confirmed association so far, the question remains whether these are warranted at this stage.

5. Updated Benefit-risk assessment

The scope of this referral procedure does not reflect efficacy data. The submitted safety data as well as safety data from the literature do **not** provide **sufficient evidence to alter the benefit risk balance** of Cervarix. However, the link between CRPS or POTS and vaccination with Cervarix needs to be further investigated (cfr section 6 Recommendations and Appendix A – Question 5).

6. Updated Recommendations

Based on the review of all available data on safety, the co-rapporteur considers that the benefit-risk balance of Bivalent HPV vaccine (types 16, 18) **remains favourable** and therefore **recommends the maintenance of the marketing authorisation**.

However, the co-rapporteur considers the risk of CRPS as a weak safety signal, and is of opinion that a causal association with HPV vaccine cannot be completely ruled out at this stage, for the following reasons:

- CRPS is probably caused by a multifactorial process, including inflammatory and immune related factors (proinflammatory neuropeptides & mediators + cytokines). An automimmunity process has also been suggested for CRPS, among other hypotheses. This may explain why the reported cases of CRPS did not display a clear clinical pattern or dose relationship;

- Paediatric CRPS can be triggered by minor trauma. However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections;

- CRPS occurs more frequently in female than male, but is most common in older women (50-70 years old) and relatively rare in childhood/adolescence.

The Co-Rapporteur BE is of the opinion that CRPS should continue to be investigated as the potential involvement of HPV vaccine in the occurrence of CRPS cannot be completely ruled out at this stage.

Regarding POTS, the Co-Rapporteur BE agrees with DK that it is possible that patients with the same symptomatology would receive different diagnoses such as Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME). The SAG was of the view that the vast majority of the cases presented in the literature and database review do not fit with the accepted definitions of POTS and would more appropriately be labelled as having features of CFS. This is likely because POTS is not a disease but a syndrome, which can be associated (or not) to a variety of conditions. However, taking into account the available data for Cervarix, the Co-Rapporteur BE remains of the opinion that there is no safety signal for POTS. However, because of the difficulty to diagnose the syndrome, the rarity of POTS fully fitting the case definition (when considering all factors of exclusion), and the variety of conditions which could be associated to POTS, monitoring of POTS in routine pharmacovigilance may be difficult.

In conclusion, the co-rapporteur is of the opinion that further monitoring of CRPS and POTS in PSUR, including an extensive review of the literature and a follow-up of reported cases of CRPS and POTS, should be performed. Since POTS and CRPS remain a public concern in a number of countries, the SAG supports such an enhanced surveillance despite its opinion that there is no evidence of a signal.

Finally, it is endorsed that communication and involvement of the public and stakeholders should be considered very carefully for this referral, regarding the growing public attention on this topic. The Co-Rapporteur BE agrees that, as the persistent concerns and uncertainties in the public have already caused declines in vaccination rates, it is vital to address these concerns by using the opportunities and available tools for proactive dialogue during and after the procedure".

7. Next steps

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8. References

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Annex 1 Proposed List of Outstanding Issues

Not applicable.

Annex 2 Recommended changes to the product information

Not applicable.

Annex 3 Proposed Dear Healthcare Professional Communication

Not applicable.

Annex 4 Comments received

Comments received from [redacted]

[redacted] agrees with the overall conclusions of the PRAC Rapporteur that the benefit/risk of the HPV vaccines remains positive. [redacted] considers that the feasibility of a PASS is doubtful as the diagnoses for identifying the cases, specially on POTS, are still unclear and difficult to assess. [redacted] does not consider Cervarix Co-Rapporteur proposal in relation to further evaluation of CRPS and POTS is necessary at the moment.

Comments received from [redacted]

General comments

The [redacted] agrees with the conclusions of the Rapporteur and the Co-Rapporteur for Gardasil/Silgard. The [redacted] agrees with the Rapporteur who did not endorse the additional evaluation of CRPS and POTS. We think that the proposal of the Cervarix Co-Rapporteur is somewhat vague and leaves quite a number of questions open.

Other aspects

The data presented in this referral with the focus on Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS) do not indicate a safety signal (outside Denmark and Japan) nor could a clear clinical pattern of the cases been identified. The potential pathomechanisms (e.g. dysautonomia caused by small fiber neuropathy, autoimmune processes) are at present only hypothetical.

Regarding the data from Denmark and Japan a bias cannot be excluded and a clear causal relationship to the HPV could not be demonstrated.

Notably, symptoms for other diagnoses (e.g. CFS and fibromyalgia-like illness) are overlapping with symptoms of POTS and CRPS which complicates the analyses.

Concerning the areas for discussion with SAG and the need for a PASS discussion about feasibility of such a study is also important as the diseases are currently ill defined and symptoms overlap with other diagnoses.

Comments received from [redacted]

[redacted] supports the conclusions of the Rapporteur and Co-rapporteurs that the benefit/risk of the HPV vaccines remains positive.

[redacted] supports DHMA comment that due to differential clinical practice across countries, similar suspected ADRs to HPV vaccine are receiving different diagnoses (or indeed no clear diagnosis), which in turn may be potentially 'diluting' a safety signal.

CRPS and POTS are uncommon and frequently underreported precisely because their symptoms can mimic a large number of other possible conditions seen by practitioners from various professional backgrounds. On the other hand, many practitioners may not even be aware of the possibility that the signs and symptoms mentioned for these two syndromes can be linked to a past history of vaccination with HPV vaccine.

Therefore, since available data do not provide support for a causal relation between the HPV vaccine and CRPS or POTS, we consider that for the moment no changes to the product information, risk minimisation measures or other conditions are deemed necessary.

[redacted] endorses all the questions proposed for the meeting of the Vaccine SAG planned for the 21st October and [redacted] considers that the need for additional surveillance or even a PASS should only be considered upon the expert answers.

Comments received from [redacted]

General comment

[redacted] agree with the overall conclusions of the PRAC Rapporteurs that the benefit/risk of the HPV vaccines remains positive.

We agree with the limitations in the current data, but we do find it important not to dismiss the issue at this point but to consider studies or other activities to gain additional information in the future.

Also we find that active communication and involvement of all relevant stakeholders is key to address current and future public concerns and ensure the public confidence in the national vaccination programs.

We also have some specific comments and additional points for the further evaluation of the issues. See below.

Clinical safety

Identification of POTS cases in spontaneous reports for Gardasil:

In the search for cases coded as POTS in the database the MAH make a further selection by case definition criteria that appears too limiting. Only cases that are medically confirmed have been included, which is reasonable for a diagnosis such as POTS that cannot be expected to be verified by a consumer. 83 reports are identified as medically confirmed but out of these almost half (40 cases) are then dismissed for not meeting the case definition for POTS. It appears that they have been dismissed mainly due to lack of information in the reports. This does not appear to be in accordance with good practice, since spontaneous reports cannot be expected to describe all details for a diagnosis given to a patient. As also pointed out in the rapporteurs AR p.22, we agree that when a diagnosis is reported and verified by a HCP, this description should be accepted and used in the further work e.g. observed versus expected ratios.

We propose to add an additional question to the MAH in the list of outstanding issues, where the MAH should submit a new calculation of observed versus expected ratios based on the whole dataset.

Discussion of causality for POTS and consistency of the signal:

The main conclusion in the Danish report is not, as described in the assessment, to change focus to CFS. Rather the review highlights the necessity to evaluate combinations of symptoms rather than only performing separate evaluations of individual diagnoses. It shows that although the number of POTS cases is very high in Denmark, compared to the rest of the world, the symptom pattern seen in the Danish dataset is similar to reports submitted from other countries. Even though it cannot be shown for certain at this point, it is likely based on these data, that patients with the same symptomatology would receive different diagnoses in different member states e.g. POTS in DK and CFS/ME in others. This consideration is important for the discussion of consistency regarding the POTS signal, where it is stated that the finding of the majority of POTS cases in Denmark does not support a causal relationship. We do not agree with this conclusion based on the data.

Risk Management Plan/ Post-authorisation Safety Studies/ Conditions

Need for further studies regarding the signal for POTS:

We agree with the conclusion from the rapporteurs and also state in the Danish report, that the data from spontaneous reports cannot be used to provide evidence for a causal relationship between symptoms and vaccination.

However in view of the methodological limitations of the data available and the fact that the observed cases did exceed the expected cases, especially in Japan and Denmark, the conclusions should be cautious and the signal cannot be dismissed either based on the current evidence.

We recommend that the vaccine SAG and expert meeting include a discussion of the need and possibilities to design appropriate PASS studies to explore POTS further. Similar question as Q3 regarding CRPS.

Other aspects

Communication and involvement of the public and stakeholders should be considered very carefully for this referral.

The persistent concerns and uncertainties in the public are seen in several member states as apparent from the ongoing EMA media surveillance and have already caused declines in vaccination rates.

It is vital to address these concerns by using the opportunities and available tools for proactive dialogue during and after the procedure.

Comments received from [redacted]

The comprehensive evaluation and conclusions of the Rapporteurs are endorsed. Based on the current evidence the B-R remains unaltered and no update of the product information is warranted at the moment.

The added value of additional analyses (i.e. PASS) requires further discussion in the SAG.

We acknowledge the difficulty with regard to the feasibility of a PASS study, however the feasibilities for a PASS might be different for CRPS in comparison with a PASS for POTS.

<u>Co-Rapporteur's conclusions following the comments from MS:</u>

[redacted] *and* [redacted] *agree with the opinion of the Rapporteur and Co-Rapporteurs that the benefit/risk of the HPV vaccines remains positive.*

[redacted] *and* [redacted] *do not support the requirement of an additional evaluation of CRPS and POTS. However,* [redacted] *and* [redacted] *agree that the need of further surveillance or a even a PASS should be discussed with the experts during the SAG meeting of 21st October 2015. Besides,* [redacted] *supports the need for further investigation of CRPS and POTS, via studies or other activities.*

The Co-Rapporteur BE acknowledges the comments from MS. Without any new data, BE still considers the risk of CRPS as a weak safety signal, and is of opinion that a causal association with HPV vaccine cannot be completely ruled out at this stage, for the following reasons:
- CRPS is probably caused by a multifactorial process, including inflammatory and immune related factors (proinflammatory neuropeptides & mediators + cytokines). An automimmunity process has also been suggested for CRPS, among other hypotheses. This may explain why the reported cases of CRPS did not display a clear clinical pattern or dose relationship;
- Paediatric CRPS can be triggered by minor trauma. However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections;

- CRPS occurs more frequently in female than male, but is most common in older women (50-70 years old) and relatively rare in childhood/adolescence.
In conclusion, the Co-Rapporteur BE is of the opinion that CRPS should continue to be investigated as the potential involvement of HPV vaccine in the occurrence of CRPS cannot be completely ruled out at this stage. Further monitoring in PSUR can be considered. However, due to the complexity of the disease, the risk of underdiagnosis, and the existence of different diagnostic criteria, routine pharmacovigilance may not be the most appropriate option. In this view, a PASS might be considered. However, the Co-Rapporteur fully agrees that the feasibility and the relevance of such a study should firstly discussed at the SAG. Of note, a PASS could also provide some answers to the growing public attention to the HPV vaccine safety.
Regarding POTS, the Co-Rapporteur BE agrees with [redacted] *that it is possible that patients with the same symptomatology would receive different diagnoses such as Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME). This is likely because POTS is not a disease but a syndrome, which can be associated (or not) to a variety of conditions. However, taking into account the available data for Cervarix, the Co-Rapporteur BE remains of the opinion that there is no safety signal for POTS. However, because of the difficulty to diagnose the syndrome, the rarity of POTS fully fitting the case definition (when considering all factors of exclusion), and the variety of conditions which could be associated to POTS, monitoring of POTS in routine pharmacovigilance may be difficult. In this regards, the requirements of a future monitoring (even in routine pharmacovigilance) should be better defined (e.g. by identifying identify a set of relevant autonomic disorders to monitor). This may be discussed with the SAG's experts.*
Finally, it is endorsed that communication and involvement of the public and stakeholders should be considered very carefully for this referral, regarding the growing public attention on this topic. The Co-Rapporteur BE agrees that, as the persistent concerns and uncertainties in the public have already caused declines in vaccination rates, it is vital to address these concerns by using the opportunities and available tools for proactive dialogue during and after the procedure.

Appendix A Detailed assessment of the MAH's responses

Question 1

The MAHs should provide a cumulative review of available data from clinical trials, post-marketing and literature in order to evaluate the cases of CRPS and POTS with their product.

Review an case detection methods should be clearly described and the evaluation should discuss whether the reported cases fulfill published or recognized diagnostic criteria.

Introduction

MAH's response

Continuous management of safety signals is an integral part of GSK's Pharmacovigilance system. We take a proactive and holistic approach to signal detection and evaluation. This includes regular review of emerging safety data from clinical studies and regular signal detection for marketed products based on an aggregate review, using disproportionality analysis, of adverse event reports from the GSK global safety database. As signals may also emerge from literature reviews, enquiries from external sources, epidemiological studies, registry data, pre-clinical information (e.g., animal toxicology, pharmacology) and competitor data, these sources are also interrogated, as appropriate, when evaluating signals at GSK. All signals from all sources are prioritised for evaluation and at the same time, signals meeting criteria for expedited reporting are communicated to the regulatory authorities.

Reports of CRPS (Complex Regional Pain Syndrome) and POTS (Postural Orthostatic Tachycardia Syndrome) following vaccination with Cervarix are adverse events (AEs) that have been reviewed in the context of Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) that are shared to regulatory agencies worldwide according to local regulation.

As requested in response to the Article 20 procedure, GSK has conducted a review of all available data from clinical trials, as well as from spontaneous, post-marketing case reports to evaluate the potential risk of CRPS and POTS with Cervarix. Case reports identified in the scientific literature are also entered in the GSK global safety database as a post-marketing case.

Since clinical trials are designed with a control/comparator group, for the purpose of this exercise, analysis of clinical trial safety data is conducted separately to allow a comparison of the reporting rate between subjects vaccinated with HPV and subjects vaccinated with a control/comparator vaccine(s). Hence, analysis of serious and nonserious AEs reported in the clinical programme is presented in the response to Question 2.

Since the first launch of Cervarix (May 2007) up to the data lock point of 15 June 2015, more than 24,000 case reports have been recorded in the GSK global safety database following vaccination with Cervarix in post-marketing setting.

CRPS

MAH's response

CRPS has been described as locally appearing painful conditions following a trauma which chiefly occur distally and exceed in intensity and duration of the expected clinical course of the original trauma. It occurs slightly more often in the upper extremities. Fracture is the most common initial event (43%). Women are affected 3.4 times more often than men with mean age at diagnosis of 52 years (De Mos , 2007). The clinical entity of CRPS remains incompletely understood. CRPS is subdivided into CRPS-I

and CRPS-II, reflecting the absence or presence of documented nerve injury, respectively. Despite this traditional diagnostic distinction, signs and symptoms of the two CRPS subtypes are similar, and there is no evidence that they differ in terms of pathophysiologic mechanisms or treatment responsiveness (Bruehl , 2010; Marinus 2011). The diagnosis is only based on clinical criteria, i.e. presence of pain, as well as sensory, vasomotor, pseudomotor/oedema, trophic, and motor disturbances (Harden et al. 2010), as presented in Table 1.

Table 1: Budapest clinical diagnostic criteria for CRPS

(1) Continuing pain, which is disproportionate to any inciting event

(2) Must report at least one symptom in three of the four following categories:

- Sensory: reports of hyperesthesia and/or allodynia
- Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
- Pseudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

(3) Must display at least one sign at time of evaluation in two or more of the following categories:

- Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
- Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
- Pseudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

(4) There is no other diagnosis that better explains the signs and symptoms.

The GSK global safety database was searched using the following criteria:

Data lock point(s): 15 June 2015

Report types: All spontaneous and post-marketing case reports

Cervarix was reported as a suspect vaccine.

A stepwise approach in the analysis of cases was performed: (1) analysis of case reports that included the MedDRA Preferred Terms (PTs) of CRPS, and (2) Analysis of case reports that included signs and symptoms of CRPS (suspected cases of CRPS). Outcome of this evaluation is outlined below:

1. Analysis of cases that included the MedDRA Preferred Term (PT) of CRPS

Since launch (17 May 2007) until 15 June 2015, a total of 49 case reports were identified in the GSK global safety database that included the MedDRA PT of CRPS. This corresponds to a reporting rate of 0.086 per 100,000 doses distributed worldwide. All individual cases were reviewed and classified according to the established case definition by Harden et al 2010, as described above.

In summary, five cases, that reported disproportionate continuous pain, allodynia and other signs of autonomic system disturbance in an injected limb, were identified as confirmed cases of CRPS as

presented in Table 2 including the company comments that summarizes the medical assessment of each case.

Thirty-seven (37) cases were classified as unconfirmed cases of CRPS and six as unlikely cases of CRPS according to the established case definition for CRPS. Details of the assessment for these cases are presented in Annex 1.

One case from Japan that was identified in an article contains insufficient information to perform further assessment (e.g. subject's details and adverse events experienced). It was classified as unassessable case and therefore excluded from the assessment.

Table 2: Confirmed cases of CRPS according to the established case definition of CRPS by Harden et al 2010 (n=5)

Argus Case ID	Age / Gender	Country	List of events (MedDRA PTs)	Total number of doses received (dates of vaccination)	Dose numbers administered after onset of pain	Case Outcome	List of Medical Conditions	*Company Comments*
[redacted]	46/F	[redacted]	Bone atrophy, Periarthritis, Arthritis, Bursitis, Synovitis, Synovectomy, Arthralgia, Injection site pain, Injection site movement impairment, Injected limb mobility decreased, Musculoskeletal pain, Musculoskeletal stiffness, Joint swelling, Polyarthritis, Pain, Incorrect route of drug administration, Complex regional pain syndrome, Injection site erythema, Fluid retention, Myositis, Muscular weakness, Pain in extremity, Injection site swelling, Tendonitis, Red blood cell sedimentation rate increased, C-reactive protein increased, Rotator cuff syndrome, Synovial disorder, Inflammation, Excessive granulation tissue, Fibrosis, Hyperaesthesia, Temperature regulation disorder, Oedema, Hyperhidrosis, Hypohidrosis, Dystonia, Joint contracture, Soft tissue disorder	3 (06-Apr-10, 13-May-10, 19-Oct-10)	All 3 doses administered; the onset of injected limb mobility decreased was at 196 days after the first dose. Duration of AEs was not reported.	Unknown	Current Condition: Allergy to fermented products	*Fulfils diagnostic criteria of CRPS. The subject experienced intense persistent pain, oedema, decreased range of motion of vaccinated limb. However, vaccine was administered at wrong place, close to acromion and the subject was concurrently diagnosed with bursitis and synovitis. The events can be considered related to the method of administration (maladministration). Usual daily activities were affected.*
[redacted]	12/F	[redacted]	Oedema peripheral, Pain in extremity, Musculoskeletal pain, Hypoaesthesia, Injected limb mobility decreased, Pyrexia, Skin discolouration, Pain, Injection site irritation, Peripheral coldness, Movement disorder, Back pain, Injection site paraesthesia, Extensive swelling of vaccinated limb, Complex regional pain syndrome, Gait disturbance, Hyperhidrosis, Injection site pain, Injection site swelling, Allodynia, Oedema, Diplopia, Swelling, Dysgeusia, Seizure, Dyscalculia, Abnormal behaviour, Screaming, Platelet count decreased, Dissociation, Photophobia, Nausea, Anxiety, Headache, Pruritus, Rash, Dysphagia, Injection site hypoaesthesia, Peripheral swelling, Vomiting, Arthralgia, Myalgia, Memory impairment, Sleep disorder, Fatigue, Feeling abnormal, Amnesia, Moaning, Fall, Neuralgia, Mental impairment, Abnormal sleep-related event, Nervous system disorder, Tremor, Gaze palsy, Asthenia, Depressed level of consciousness, Abnormal dreams, Malaise, Abdominal pain, Loss of consciousness, Dyskinesia, Visual acuity reduced, Dizziness, Judgement impaired, Anaphylactic reaction, Menstruation irregular, Limb discomfort	2 (16-Sep-11, 19-Oct-11)	2 doses administered; onset of oedema, oedema peripheral and pain in extremity at 33 days after the first dose; the onset of hypoaesthesia at 34 days after the first dose; duration of AEs were reported to be >1200 days.	Recovering/ Resolving	Historical Condition:Appendicitis, Temporomandibular joint syndrome, Enteritis infectious, Appendicectomy	*Fulfils diagnostic criteria of CRPS. Intense pain, allodynia was mentioned, extensive swelling, hyperhidrosis, skin discoloration of vaccinated limb. Usual daily activities were affected. Medical history includes abdominal pain with diagnosis of chronic appendicitis, and occasional abdominal pain after surgery.*
[redacted]	14/F	[redacted]	Injection site pain, Injected limb mobility decreased, Abasia, Loss of consciousness, Shock, Guillain-Barre syndrome, Peripheral swelling, Pallor, Grip strength decreased, Headache, Musculoskeletal pain, Nausea, Asthenia, Syncope, Coordination abnormal, Dizziness, Oedema peripheral, Photopsia, Malaise, Urticaria, Insomnia, Dyspnoea, Hypoaesthesia, Anxiety, Confusional state,	3 (08-Aug-11, 06-Sep-11, 07-Feb-12)	3 doses administered; the onset of injected limb mobility decreased at 29 days after the first dose; the onset of hypoaesthesia, muscular weakness, oedema	Not Recovered/Not Resolved		*Fulfils diagnostic criteria of CRPS. Continuous sever pain was reported in vaccinated arm, weakness, and coldness of upper and lower extremities, lower limb oedema, pain in the chest and leg, dyspnoea, hyperpnoea, slight fever, stomatitis, worsening of painful menses, and taste disturbance. Initially, no symptoms*

Argus Case ID	Age / Gender	Country	List of events (MedDRA PTs)	Total number of doses received (dates of vaccination)	Dose numbers administered after onset of pain	Case Outcome	List of Medical Conditions	*Company Comments*
			Depressed mood, Dysgeusia, Decreased appetite, Complex regional pain syndrome, Hyperventilation, Chest pain, Peripheral coldness, Feeling cold, Abdominal pain, Pain, Muscular weakness, Muscle atrophy, Neuralgia, Muscle spasms, Nervous system disorder, Pain in extremity, Pyrexia, Orthostatic intolerance, Menstruation irregular, Memory impairment, Arthralgia, Myalgia		peripheral and pain in extremity was at >555 days after the first dose; complex regional pain syndrome was reported at 605 days after the first dose. Duration of reported AEs was unknown.			*related to local presentation of CRPS were reported. Usual daily activities were affected.*
[redacted]	14/F	[redacted]	Complex regional pain syndrome	1 (date not reported)	1 dose administered; the date of vaccination was not reported, the onset of CRPS at 1 day after vaccination with unknown date and duration.	Resolved with Sequelae	Historical Condition:Gastritis, No adverse event	*Fulfils diagnostic criteria of CRPS. Intense pain, increasing in severity, swollen (oedema) arm, sweating, with intermittent cold, warm hand, blue discolouration and restricted hand movement of vaccinated limb. Usual daily activities were affected.*
[redacted]	12/F	[redacted]	Complex regional pain syndrome, Paraesthesia, Muscular weakness, Pain in extremity, Pallor, Skin discolouration, Body temperature decreased, Oedema, Injected limb mobility decreased	1 (date not reported)	1 dose administered; the date of vaccination and the onset of pain symptoms were not reported; CRPS was reported to have lasted for 210 days.	Resolved	Current Condition:Headache	*Fulfils diagnostic criteria for CRPS with symptoms disproportionate to inciting events, as paraesthesia progressing to left arm weakness and pain, skin discoloration, temperature changes, oedema and decreased limb mobility. It was not reported that daily activities were impacted*

2. Analysis of cases that included signs and symptoms of CRPS (suspected cases of CRPS)

For this analysis, a stepwise methodology was followed to evaluate cases reporting signs and symptoms of CRPS to determine potential undiagnosed or unrecognized cases of CRPS in the GSK global safety database for Cervarix.

To retrieve cases for evaluation, symptoms described in the Budapest criteria of CRPS (Harden et al. 2010) were matched to the MedDRA PTs as presented in Table 3.

Table 3: Criteria established by Harden et al 2010 matched to the MedDRA Preferred Terms (PTs)

Symptoms of CRPS, Harden, 2010	MedDRA PTs
Pain: Continuing pain disproportionate to vaccination	Pain; Pain in extremity
Sensory: Allodynia deep pressure pain, Allodynia pain after movement, Allodynia after light touch, Hyperesthesia, Hypoesthesia, Hyperalgesia, Hypoalgesia	Allodynia, Hyperaesthesia, Hypoaesthesia, Sensory disturbance, Skin burning sensation
Vasomotor: Color change/difference, temperature difference	Skin discolouration, Skin hyperpigmentation, Skin hypopigmentation, Skin atrophy, Temperature difference of extremities, Skin warm, Skin depigmentation, Skin dystrophy
Pseudomotor /oedema: Transpiration disturbance, Edema	Oedema, Oedema peripheral, Hyperhidrosis, Hypohydrosis, Cold sweat, Skin oedema
Trophic: Hair growth change, Nail growth change, Trophic skin disturbance	Hair growth abnormal, Nail growth abnormal, Onychoclasis
Motor: limitation of movement, Limitation of strength, Dystonia, Tremor, Bradykinesia	Injection site movement impairment, injected limb mobility decreased, Muscular weakness, Dystonia, Tremor, Bradykinesia, Motor dysfunction

a) The GSK global safety database was queried to identify cases which reported MedDRA PT of "Pain" or "Pain in extremity'. As a result, a total of 2,001 were identified.

b) It is expected that some subjects would report pain or pain in extremity, as a substitute of injection site pain which should resolve within 2 weeks at maximum. Therefore, only cases of pain or pain in extremity with duration of more than two weeks were included for further analysis. This subset of data was classified as 'longterm pain'. Case reports that also included the MedDRA PT of CRPS were excluded in this analysis since these cases had been analyzed separately as described above. As a result, a total of 1,580 cases were included in the further step.

c) The subset of 'long-term pain' cases was used to identify cases with other possible symptoms of CRPS, as below:

i. Subset of 'long-term pain' + sensory symptoms

ii. Subset of 'long-term pain' + vasomotor symptoms

iii. Subset of 'long-term pain' + pseudomotor symptoms

iv. Subset of 'long-term pain' + trophic symptoms

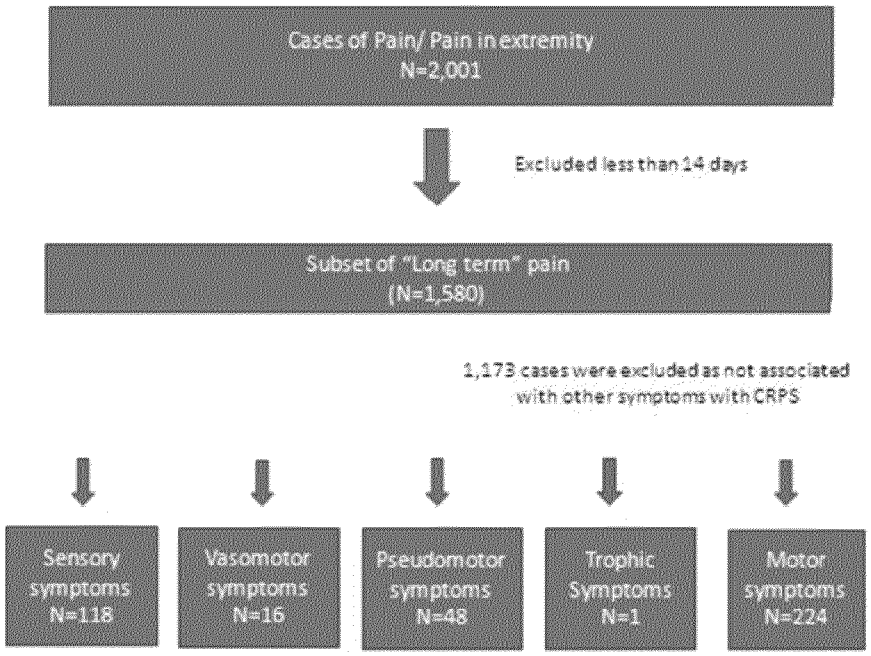
v. Subset of 'long-term pain' + motor symptoms

vi. Subset of 'long-term pain' + all symptoms

d) Cases identified in step c were reviewed and assessed against the established case definition of CRPS by Harden 2010.

e) Results of this search are presented in Figure 1.

Figure 1 CRPS: Search strategy and number of cases identified



In summary, for the cases that reported a combination of pain or pain in extremity:

- 118 cases were associated with sensory symptoms. Of these,
  - 45 cases were reported in the context of concurrent diseases such as neuropathy peripheral, Guillan-Barre syndrome, fibromyalgia, arthritis and other rheumatoid diseases.
  - character of pain and location of pain and sensory symptoms were missing in 68 cases
  - 3 cases were suggestive of injection site reactions that persisted beyond two weeks,
  - diagnosis of CRPS was not confirmed following investigation in 1 case
  - CRPS could not be excluded in 1 case, as severe persistent pain, numbness and burning sensation were all reported in vaccinated limb, the subject was treated with analgesics, it was also reported that pain spread over the body. As only pain in extremity and sensory disturbance were present and therefore a diagnosis of CRPS could not be confirmed.
- 16 cases were associated with vasomotor symptoms. Of these,
  - 1 case was reported in the context of concurrent disease as neuropathy peripheral,
  - 2 cases were suggestive for injection site reaction that persisted beyond two weeks
  - for 12 cases, character of pain and location of pain and vasomotor symptoms were missing or the information provided did not fit with the definition of CRPS,
  - CRPS could not be excluded in 1 case, as pain and skin discoloration of vaccinated limb were reported, the events worsen 1 day after vaccination. No further information has been reported to confirm a CRPS diagnosis.

- 48 cases were associated with pseudomotor symptoms. Of these,
  - 13 cases were reported in the context of concurrent diseases, such as neuropathy peripheral, GBS, juvenile arthritis, paralysis.
  - 25 cases were suggestive of injection site reaction that persisted beyond two weeks
  - for 10 cases, the character of pain and location of pain and pseudomotor symptoms were missing or the information provided did not fit with the definition of CRPS.
- One case was associated with trophic symptoms. This case was reported in the context of a concurrent disease – cutaneous vasculitis.
- 224 cases were associated with motor symptoms. Of these,
  - 54 cases were reported in the context of concurrent disease, such as juvenile arthritis, paralysis, fracture, GBS, herpes zoster, periatritis, phlebitis etc,
  - 136 cases were suggestive of injection site reaction that persisted beyond two weeks,
  - For 33 cases, character of pain and location of pain and motor symptoms were missing or the information which provided did not fit with the definition of CRPS.
  - CRPS could not be excluded in 1 case, as pain and injected limb mobility decreased were reported in vaccinated limb with decreased grip strength. The subject was treated with pregabalin with slight improvement. No further information has been reported to confirm a CRPS diagnosis.

As a result of this review, 3 suspected cases of CRPS were identified that reported a combination of pain or pain in extremity, however the level of information including the absence of other required symptoms of CRPS and objective confirmation of these symptoms do not allow to confirm a diagnosis of CRPS.

In summary, no cases of CRPS were identified as confirmed from this analysis.

3. Additional analysis following the search criteria suggested by Sanofi Pasteur/Merck Sharp and Dohme (SP/MSD).

Although both GSK and SP/MSD agreed to use the same CRPS case definition based on Harden 2010, slight differences remained on CRPS search methodology regarding the list of MedDRA PTs and its combination. GSK decided to keep the search methodology used in previous analyses conducted by the Company, previously communicated to the PRAC and published in the medical literature (Huygen 2015). While it is acknowledged that no significant differences would result in using both search methodologies, an additional analysis was performed based on search methodology by SP/MSD to ensure that all suspected cases of CRPS are retrieved, as outlined below.

Step 1:

Table 4 presents five groups that included a combination of MedDRA PTs representing symptoms of CRPS. These five groups were used in the 5 queries, as described below.

Table 4: SP/MSD criteria: MedDRA PTs representing symptoms of CRPS

Groups	MedDRA PTs
Group A	back pain, flank pain, musculoskeletal pain, neck pain, pain in extremity, pain
Group B	hyperaesthesia, allodynia, hypoaesthesia
Group C	feeling hot, skin discoloration, skin hyperpigmentation, skin hypopigmentation, skin warm, feeling cold, cold sweat, onychoclasis, hair growth abnormal, peripheral coldness, skin atrophy
Group D	oedema, hyperhidrosis, cold sweat
Group E	muscular weakness, tremor, dystonia, motor dysfunction, orthostatic tremor, mobility decreased, abasia , paresis

Step 2:

Five queries were run using the logic displayed below:

Query #1: Group A AND Group B AND Group C AND Group D

Query #2: Group A AND Group B AND Group D AND Group E

Query #3: Group A AND Group B AND Group C AND Group E

Query #4: Group A AND Group C AND Group D AND Group E

Query #5: Group A AND Group B AND Group C AND Group D AND Group E

As a result of these queries, 23 cases were identified in the GSK global safety database.

Of these cases:

- 10 cases contained the MedDRA PT of CRPS (these cases were included in the first analysis provided above),
- For 5 cases, the description and/or location of pain was missing or the information provided was limited and did not fit with the definition of CRPS
- The remaining cases were reported with concurrent diagnosis, such as paralysis, fibromyalgia, epilepsy, nervous system disorder, etc.

No additional cases of suspected CRPS were identified, as a result of this analysis.

Based on the search methodology by SP/MSD, 3 cases were identified that were not included in the GSK analysis. For 2 cases, the symptom of pain or pain in extremity lasted less than 2 weeks and one case reported back pain but the MedDRA PTs of pain or pain in extremity was not reported.

Conclusion

Altogether, using different search methodologies to retrieve all case reports indicative of CRPS in the GSK global safety database for Cervarix (total N = > 24,000 spontaneous and literature reports) and following over 57 million doses of Cervarix distributed globally, five case reports fulfilled the criteria of CRPS according to the established case definition (Harden 2010). A broader search strategy using more sensitive but less specific event terms in order to identify suspected cases of CRPS, including an additional search based on SP/MSD search criteria, did not identify additional cases in these analyses.

Given the heightened public concern regarding the safety of HPV vaccines in Japan, triggered by the case reports of CRPS in Japan in 2013, GSK has since conducted comprehensive analyses with regard to CRPS, including consultation with an independent expert panel for 'pain'. Following similar methodology to that outlined in response to Question 1 and after the preliminary review of the

identified CRPS cases by a GSK safety physician, the two independent external experts were provided with the individual clinical narratives of identified cases for review using the same case definition. The assessment of cases by GSK and the results of the quantitative analyses were only shared with the experts once their own separate assessments of individual cases were completed. Results of this safety evaluation have just been published (Huygen 2015) and are very much in line with the outcome of these investigations.

In conclusion, it is GSK's opinion that the outcome of this analysis is not sufficient to establish a causal association between CRPS and vaccination with Cervarix.

CRPS will remain under safety surveillance, as described in the current Risk Management Plan for Cervarix (version 10.1), the results of ongoing safety evaluation will be discussed in the annual Periodic Safety Update Report cycles.

Assessor's comments

Cases with PT=CRPS

In total, 49 cases with PT CRPS have been retrieved by GSK since the first launch of Cervarix (May 2007) until the DLP of 15 June 2015. Diagnosis of CRPS cases is hampered due to the variety of signs and symptoms in highly variable combinations with a variable progression over time and the absence of a gold standard test to confirm CRPS. The Budapest clinical diagnostic criteria for CRPS of Harden et al. (2010) were applied to assess each case. The Co-Rapporteur categorized the cases according to the following scheme:

PT CRPS	Criteria Harden followed: YES	Criteria Harden followed: NO/UNKNOWN
Diagnosed cases	**2**	**12**
Suspected cases	**0**	**9**
Mentioned cases	**3**	**23**

1/ In 5 out of 49 cases, the diagnostic criteria for CRPS of *Harden et al. (2010)* were met ([redacted], [redacted] and can be considered as CRPS cases. **In 3 of these 5 cases ([redacted]), the involvement of Cervarix in the occurrence of CRPS cannot be ruled out due to:**

- a strong temporal relationship between the events and administration of the vaccine (same day to less than 2 weeks),

- the absence or unknown relevant medical history

- the absence of other events which might explain the symptoms.

Details of these 3 CRPS cases:

The age group affected ranged from 12 to 20 years of age, one report originated from Japan, the other two reports from UK. The occurrence of the events varied from being present after first or third dose. Outcome was unknown or positive (resolved or resolved with sequelae) in respectively one and two reports. In one case the events were considered serious due to disability or incapacity. CRPS has been diagnosed in one report, one week after the administration of the first dose of Cervarix.

Two remaining cases describe either events occurring after maladministration of the vaccine [redacted] or some events occurring within 1 hour after vaccination which would expect to be taken place after a certain delay (i.e. numbness of lower extremities, generalized pain) [redacted]. In these cases, no conclusion can be made.

2/ The remaining 44 cases can be considered as potential CRPS cases, because of insufficient information regarding the diagnostic criteria or incompletely fulfilled diagnostic criteria of Harden et al.

Nevertheless, 12 cases were **still *diagnosed or reported by a physician***. **In 6 out of the 12 *diagnosed* cases [redacted], the involvement of Cervarix in the occurrence of a *potential* CRPS cannot be ruled out due the same reasons mentioned above.**

Details of these 6 potential CRPS cases:

The age group affected ranged from 13 to 16 years of age; in one case age was not specified but ranged between 10-19 years of age. These cases were originated from Japan, except one from UK [redacted]. The events started within the first month or earlier after administration of the vaccine. Half of the cases presented with a positive outcome (recovering/resolving), the remaining cases presented with an unknown outcome (n=2) or resulted in unresolved events (n=1). In half of the cases the events were considered serious due to hospitalization or disability/incapacity. In half of the cases time of diagnosis was unspecified, in the other half it varied from 1 week to 1 month after vaccination.

For the following cases it is not possible to draw a conclusion:

In one case differential diagnosis of fibromyalgia with somatoform disorder was made. Another case was confounded by other events which might explain the symptoms (Guillain-Barré syndrome). Other cases did not report a strong temporal relationship with the vaccination (2 to 4 months after the second dose, n=2) or did not specify the time to onset of the events (n=1). In 1 case diagnosis was made 1 day after vaccination which is unlikely as CRPS diagnosis is made after exclusion of other diseases and no specific diagnostic test is available.

In 9 out of the 44 cases, CRPS was ***suspected.*** **In only 1 case [redacted] the involvement of Cervarix in the occurrence of a *potential* CRPS cannot be ruled out due to the same reasons mentioned above. Events occurred in a 14 years old girl starting within 1 month after the first dose. Outcome of the events is unknown, nevertheless the case is considered non-serious.**

In the remaining cases (n=8), other diseases could not be ruled out, such as fibromyalgia (n=2), psychosomatic or psychological disease (n=2), myositis (n=1) and/or temperal relationship was not strong (2 to 6 months after vaccination) (n=2). In two cases further examination was required or planned. For these cases it is not possible to draw a conclusion.

In 23 out of 44 cases, CRPS was ***mentioned.*** **In only 1 case [redacted] the involvement of Cervarix in the occurrence of a *potential* CRPS cannot be ruled out due to the same reasons mentioned above. Events occurred in a 16 years old girl starting 1 month after the third dose. Outcome of the events is unknown, however the case is considered serious due to hospitalization and disability/incapacity.**

In the majority of the remaining cases, temporal relationship was unknown (15 out of 23 cases) or not strong (1 out of 23 cases). Other cases were poorly described (4 cases) or were diagnosed with other diseases which might explain symptoms, such as somatoform disorder (n=1), bruising (n=1) or a normal injection site reaction (n=1). For these cases it is not possible to draw a conclusion.

Cases with PT of the signs and symptoms of CRPS – SP/MSD search

As a result of the query of SP/MSD, 23 cases were identified in the GSK global safety database.

Of these cases, 10 cases contained the MedDRA PT of CRPS (these cases were included in the first analysis provided above).

In 4 cases out of 13, the occurrence of CRPS is unlikely due to temporary pain (less than 2 weeks) or other events which disappeared after 1 day.

In 9 cases out of 13, CRPS-like symptoms are described, therefore considered to be *potential* CRPS cases:

- Eight cases did not completely meet the diagnostic criteria of Harden et al. or contained insufficient information to verify the criteria (i.e. in some cases it was unknown whether pain was continuing or not). **Therefore, these cases do not allow to confirm a diagnosis of CRPS**. In 6 of these 8 cases it is not possible to draw a conclusion because of unknown time-to-onset of the events (n=2) or no strong temporal relationship with Cervarix (n=3) and/or the presence of confounders like other (suspected) diseases (n=4) (i.e. fibromyalgia, psychogenic factors) or tetanus vaccination on an unknown date (n=1). In these cases no conclusion can be made. **In 2 of the 8 cases ([redacted], [redacted] the involvement of Cervarix in the occurrence of CRPS-like symptoms cannot be excluded due to: temporal association between the events and the administration of the vaccine (events started same day after vaccination), the absence or unknown relevant medical history and the absence of other events which might explain the symptoms. In both cases, the events occurred in adolescents (13 and 16 years of age) in different countries (Japan vs. the Netherlands) with a different outcome and severity (not recovered, serious case vs. recovering, non-serious case).**

- One case fulfills the diagnostic criteria of Harden et al. 2010 but lacks information regarding time-to-onset of the events. In this case, no conclusion can be made.

Cases with PT of the signs and symptoms of CRPS – GSK search

GSK refined their search strategy by retrieving cases with pain with duration of 2 weeks or longer or pain of unspecified duration, both combined with at least one symptom in three of the four following categories: sensory, vasomotor, pseudomotor/edema, motor/trophic, as mentioned in Huygen et al. *(2015)*. As a result of this query of GSK, 5 cases were identified in the GSK global safety database.

Of these cases, 4 cases were identified that were included in the SP/MSD search.

In the remaining case, time-to-onset of CRPS-like symptoms varied from unspecified to late time-to-onset. Furthermore this case was confounded by diagnosis of Guillain-Barré syndrome. Therefore, no conclusion can be made.

Overall conclusion

In 3 CRPS cases and 10 potential CRPS cases, which were retrieved since the first launch of Cervarix (May 2007) until the DLP of 15 June 2015, the causal relationship between the administration of Cervarix and the occurrence of CRPS/potential CRPS cannot be ruled out. Whether this is due to the injection or the vaccine itself cannot be determined as in literature CRPS was also reported following venipuncture, intravenous drug administration and other vaccinations *(Richards et al. 2012; Kwun et al. 2012; Genc et al. 2005; Jastaniah et al. 2003; Bilic et al. 2013)*. However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections.

The number of CRPS cases following administration of Cervarix is considered low compared to 57 million doses of Cervarix distributed globally. The low number might be contributed by the problem of underreporting of ADRs in general, and more specifically, the difficulty of diagnosing CRPS being a complex syndrome with a variety of signs and symptoms in highly variable combinations with a variable progression over time. Furthermore, there is no gold standard diagnostic test for CRPS available, remaining CRPS as a syndrome of exclusion of other diseases with similar signs and symptoms, and no overall consensus on the clinical diagnostic criteria of CRPS *(Rockett 2014).* However the most widely accepted diagnostic criteria are the Budapest criteria described by *Harden et al. (2010).* All taken together, many patients could be undiagnosed.

POTS

MAH's response

POTS is a poorly understood cause of orthostatic intolerance resulting from cardiovascular autonomic dysfunction. POTS is distinct from the syndromes of autonomic failure usually associated with orthostatic hypotension, such as pure autonomic failure and multiple system atrophy. Individuals affected by POTS are mainly young (aged between 15 years and 40 years) and predominantly female (Marinus J et al. Clinical features and pathophysiology of complex regional pain syndrome. July 2011. The Lancet Neurology. Volume 10 (7), p637-648. Mathias 2

Case definition

The MAH is proposing to use the case definition for POTS based on the recent publications by Raj 2013 and Sheldon 2015:

Postural orthostatic tachycardia syndrome (POTS) is defined as a clinical syndrome that is usually characterized by:

(1) Frequent symptoms that occur with standing such as light headedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue which improve with recumbence

(2) An increase in heart rate of ≥30 bpm when moving from a recumbent to a standing position held for more than 30 seconds (or ≥40 bpm in individuals 12 to19 years of age) in the absence of orthostatic hypotension (>20 mmHg drop in systolic blood pressure)

(3) Symptoms last > 6 months

(4) Absence of other overt cause of orthostatic symptoms or tachycardia (e.g., active bleeding, acute dehydration, medications)

Post-marketing data

The MAH's global safety database was searched using the following criteria:

- **Data lock point(s)**: 15 June 2015
- **Report types**: All spontaneous and post-marketing case reports
- **Cervarix** was reported as a suspect vaccine.

A stepwise approach in the analysis of cases was performed: (1) analysis of case reports that included the MedDRA Preferred Terms (PTs) of POTS, and (2) Analysis of case reports that included signs and symptoms of POTS (suspected cases of POTS). Outcome of this evaluation is outlined below:

1. Analysis of case reports that contain the MedDRA PT of POTS

A total of 19 case reports were identified in the MAH's global safety database since launch until 15 June 2015.

- Five cases were identified as confirmed cases of POTS as they contain information about symptoms suggestive of POTS and confirmation of increased pulse following the different tests (mainly Schellong's test). Table 1 provides the detail description of these confirmed cases including company's medical assessment of each case.
- Thirteen cases were classified as unconfirmed cases of POTS, as no information on BP or pulse was provided.
- One case from Japan (identified in an article) that reported both CRPS and POTS is classified as unassessable for the same reason described in the CRPS analysis.

Confirmed Cases of POTS

Table 1: Confirmed cases of POTS according to case definition by Raj et al., 2013 and Sheldon et al, 2015 (n=5)

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	*Company Comments*
[redacted]	13/F	[redacted]	Pain, Pain in extremity, Headache, Arthralgia, Abdominal pain, Myalgia, Back pain, Injection site pain, Hyperhidrosis, Peripheral coldness, Tachycardia, Neuropathy peripheral, Postural orthostatic tachycardia syndrome, Menstrual disorder	0 month after 3rd dose	3 doses administered (14-MAY-2012, 26-Jun-2012, 26-Dec-2012). Duration of reported AEs was not reported.	Dermatitis atopic, Amenorrhoea; Historical Condition: Low birth weight baby	Recovering/ Resolving	*Tachycardia only was reported with positive standing test showing increase of 46 bpm at 10 minute with concurrent increase in BP. Initial BP and pulse were low. One episode of tachycardia was reported. No other reasons that could cause orthostatic hypotension were reported. No Tilt test was reported.*
[redacted]	12/F	[redacted]	Neuropathy peripheral, Illusion, Injection site pain, Dizziness postural, Dizziness, Palpitations, Malaise, Hypoaesthesia, Pain, Asthenia, Chest pain, Headache, Anxiety, Insomnia, Arthralgia, Memory impairment, Depression, Depressive symptom, Mobility decreased, Muscular weakness, Crying, Panic reaction, Dyspnoea, Nausea, Anxiety disorder, Heart rate increased, Postural orthostatic tachycardia syndrome, Orthostatic intolerance, Tremor	3 days after 2nd dose	2 doses received (15-APR-2013, 15-May-2013). Duration of reported AEs was not reported.	Intentional self-injury;Current Condition:Stress	Not Recovered/ Not Resolved	*Dizziness, palpitation were reported. No BP or pulse measurements were reported. Blood tests NOS, ECG, head MRI, EchoCG all normal including N thyroid function. Schellong's test reported to show POTS without details. No Tilt test was reported.*
[redacted]	21/F	[redacted]	Chronic fatigue syndrome, Encephalitis autoimmune, Dizziness, Status epilepticus, Throat tightness, Fatigue, Visual impairment, Abdominal distension, Decreased appetite, Nausea, Asthenia, Presyncope, Gastrointestinal disorder, Altered visual depth perception, Visual field defect, Malaise, Abdominal pain upper, Autonomic nervous system imbalance, Activities of daily living impaired, Dysstasia, Impaired work ability, Head discomfort, Postural orthostatic tachycardia syndrome, Paraesthesia, Pruritus, Mastocytosis, Tremor, Vertigo, Impaired gastric emptying, Small intestinal bacterial overgrowth, Disorientation, Vomiting	2 days after 1st dose	2 doses received (05-Mar-2009, 20-Apr-2009).	Historical Drug:TOPIRAMATE, PIZOTIFEN, METOCLOPRAMIDE, CYCLIZINE, DOMPERIDONE, MEBEVERINE	Unknown	*Dizziness, visual impairment, presyncope were reported. Increase from 68 to 120 in the morning, low pulse in supine position was observed. BP monitoring confirmed POTS features, test was conducted in the morning. Tilt test reported slight tachycardia. EEG showed sinus tachycardia. Some difference was observed in reporting test results and diagnosis, however as worst case scenario this case is considered as confirmed.*
[redacted]	15/F	[redacted]	Complex regional pain syndrome, Orthostatic intolerance, Postural orthostatic tachycardia syndrome, Pain in extremity, Tremor, Peripheral coldness	Unknown	1 dose received (date of vaccination not reported). Duration of AEs not reported.	No information reported.	Unknown	*Orthostatic intolerance was reported. Increase in heart rate of 48 bpm per minute during Schellong test was observed. No Tilt test was reported.*
[redacted]	16/F	[redacted]	Orthostatic intolerance, Postural orthostatic tachycardia syndrome, Fatigue, Headache, Monoparesis, Gait disturbance	Unknown	1 dose received (date of vaccination not reported). Duration of AEs not reported.	No information reported.	Unknown	*Orthostatic intolerance, tachycardia were reported. Increase in heart rate of 48 bpm per minute during Schellong test was observed. No Tilt test was reported.*

The individual case details including the medical assessment of each case is provided in Table 2.

Unconfirmed Cases of POTS

The company classified 13 cases as unconfirmed (see annex A of the "Responses to questions"). All cases included the MedDRA PT of POTS but the method used to diagnose the syndrome was not specified and the measure of increase in bpm was not indicated. In some cases, dates of vaccination and dates of onset were unknown. Those cases are discussed the co-Rapporteur comments section.

Table 2: Overview of case reports that included the MedDRA PT of POTS (Worldwide, DLP 15 June 2015, n=19)

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	*Company Comments*	Case categories
[redacted]	16/F	[redacted]	Urticaria, Syncope, Seizure, Pruritus, Depressed level of consciousness, Muscle spasms, Pulse absent, Erythema, Rash, Postural orthostatic tachycardia syndrome, Epileptic aura	1 day 2nd dose	2 doses received. Duration of AEs was not reported.	Historical Condition: Asthma, Syncope, Contusion	Recovered/ Resolved	*Several episodes of syncope at the same time as subject had urticaria 1 day following vaccination with the 2nd dose. The subject has a medical history of head contusion and syncope. Tilt test performed at the same time was diagnostic for POTS without any details. The subject was treated with corticosteroids and antihistamine. All events seemed to have resolved within 1 week. EEG showed epileptic activities. No work-up for other causes. No details on pulse and BP.*	unconfirmed case
[redacted]	13/F	[redacted]	Orthostatic intolerance, Fatigue, Gait disturbance, Limb discomfort, Orthostatic hypotension, Postural orthostatic tachycardia syndrome, Mental impairment, Muscular weakness, Malaise, Chronic fatigue syndrome, Learning disorder, Feeling abnormal	5 months after 3rd dose	3 doses received (14/10/2010, 11/11/2010, 28/04/2011). Onset of orthostatic intolerance event at around 5 months after the 3rd dose that lasted for 637 days.	No information reported.	Recovering/ Resolving	*Orthostatic intolerance and hypotension were reported. No test confirming the DS, an unspecified orthostatic test was mentioned without any details. PET with normal findings, duration of the events longer than 6 months. No work-up for other causes. No details on pulse and BP. No Tilt test was reported.*	unconfirmed case
[redacted]	13/F	[redacted]	Post viral fatigue syndrome, Malaise, Limb discomfort, Pyrexia, Vomiting, Abdominal pain lower, Myalgia, Fatigue, Headache, Blood iron decreased, Menstruation irregular, Menorrhagia, Allergy to animal, Skin papilloma, Lethargy, Nasopharyngitis, Influenza, Decreased activity, Chills, Oropharyngeal pain, Rash generalised, Arthralgia, Hypoaesthesia, Dyspnoea, Emotional disorder, Mood altered, Dizziness, Menstrual disorder, Paraesthesia, Peripheral coldness, Hyperhidrosis, Alopecia, Food intolerance, Nausea, Dyspepsia, Disturbance in attention, Memory impairment, Insomnia, Increased tendency to bruise, Photophobia, Hypersomnia, Tachycardia, Postural orthostatic tachycardia syndrome, Gastrooesophageal reflux disease, Confusion	0 month after 2nd dose	2 doses received (date of vaccination was not reported); duration of AEs was not reported.	Current Condition:Seasonal allergy, Drug hypersensitivity; Historical Condition: No adverse event	Unresolved	*Decreased activity, tachycardia, dizziness were reported. No BP or pulse or diagnostic tests, including Tilt test were reported. Medical history included low Ferrum in blood test.*	unconfirmed case

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	*Company Comments*	Case categories
[redacted]	12/F	[redacted]	Seizure, Seizure like phenomena, Malaise, Pain, Headache, Influenza like illness, Dysstasia, Pain in extremity, Dizziness, Nausea, Viral infection, Nasopharyngitis, Oropharyngeal pain, Fatigue, Post viral fatigue syndrome, Chest pain, Muscle spasms, Hot flush, Nervousness, Asthenia, Chest discomfort, Dyspnoea, Abdominal pain upper, Syncope, Postural orthostatic tachycardia syndrome, Gastrointestinal disorder	1 day after 2 dose	2 doses received (date of vaccination was not reported); onset of Postural orthostatic tachycardia syndrome was reported to be >3 years after vaccination.	Historical Condition: Post viral fatigue syndrome	Unknown	*Dizziness, syncope were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]	13/F	[redacted]	Lethargy, Fatigue, Tachycardia, Myalgia, Food intolerance, Memory impairment, Menstrual disorder, Hypoaesthesia, Abdominal pain lower, Oropharyngeal pain, Alopecia, Contusion, Dyspepsia, Allergy to animal, Rash, Influenza like illness, Chest pain, Pyrexia, Increased tendency to bruise, Chronic fatigue syndrome, Photophobia, Postural orthostatic tachycardia syndrome, Headache, Peripheral coldness, Dyspnoea, Hypersomnia, Malaise, Paraesthesia, Post viral fatigue syndrome, Skin papilloma, Nausea, Menorrhagia, Gastrooesophageal reflux disease, Arthralgia, Hyperhidrosis, Disturbance in attention, Insomnia, Dizziness postural	1 week after dose 3	Dates of vaccination were not reported. Duration of AEs was not reported.	Current Condition: Seasonal allergy; Historical Drug:CERVARIX	Unknown	*Consumer case. Tachycardia, fatigue and disturbance in attention were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]	16/F	[redacted]	Loss of consciousness, Unresponsive to stimuli, Headache, Dizziness, Malaise, Chronic fatigue syndrome, Confusional state, Gait disturbance, Arthralgia, Vision blurred, Feeling hot, Musculoskeletal stiffness, Photosensitivity reaction, Hyperhidrosis, Post viral fatigue syndrome, Abdominal pain, Insomnia, Depressed mood, Neck pain, Musculoskeletal pain, Aggression, Agnosia, Seizure, Consciousness fluctuating, Oropharyngeal pain, Gingival pain, Swelling, Tonsillar hypertrophy, Tonsillitis, Infection susceptibility increased, Bedridden, Herpes zoster, Menstrual disorder, Postural orthostatic tachycardia syndrome, Syncope, Dysphagia, Disorganised speech, Hyperacusis	0 days after 3rd dose	Complete dates of vaccination were not reported. Duration of AEs was not reported.	Historical Drug: DTPA VACCINE, CERVARIX	Unknown	*Consumer case. Repetitive episodes of syncope with onset of 0 days after 3rd dose. BP and pulse at several occasions were reported as normal. Tilt test was reported as without abnormal results.*	unconfirmed case

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	*Company Comments*	Case categories
[redacted]	12/F	[redacted]	Malaise, Dizziness, Chest discomfort, Influenza like illness, Headache, Syncope, Nasopharyngitis, Oropharyngeal pain, Dysstasia, Fatigue, Pain in extremity, Gastrointestinal disorder, Viral infection, Post viral fatigue syndrome, Abdominal pain upper, Hot flush, Seizure like phenomena, Pain, Chest pain, Chronic fatigue syndrome, Asthenia, Postural orthostatic tachycardia syndrome, Dyspnoea, Nervousness, Muscle spasms, Nausea	0 month after 2nd dose	Complete dates of vaccination were not reported. Reported onset of dizziness at 1065 Days after last dose.	Historical Condition: Post viral fatigue syndrome	Unknown	*Consumer case. Syncope and fatigue were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]	13/F	[redacted]	Postural orthostatic tachycardia syndrome, Orthostatic hypotension, Autonomic nervous system imbalance, Fatigue, Malaise, Presyncope	1 month after 2nd dose	Dates of vaccination were not reported. Duration of AEs was not reported.	Historical Drug:Cervarix	Unresolved	*Orthostatic hypotension, fatigue and presyncope were reported No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]		[redacted]	Pain in extremity, Viral infection, Vomiting, Dizziness, Pyrexia, Oropharyngeal pain, Fatigue, Rash, Asthenia, Gait disturbance, Pallor, Nausea, Chronic fatigue syndrome, Postural orthostatic tachycardia syndrome, Somnolence, Malaise, Autonomic nervous system imbalance, Chest pain, Abdominal pain, Dyspnoea, Movement disorder	2 weeks after 2nd dose	Dates of vaccination were not reported. Duration of AEs was not reported.	No information reported.	Unknown	*Dizziness and fatigue were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]	12/F	[redacted]	Dizziness, Syncope, Pyrexia, Chronic fatigue syndrome, Dyspnoea, Postural orthostatic tachycardia syndrome, Chest pain, Fatigue, Hypokinesia, Pain	0 days after unknown dose	Vaccinated on 25-Sept-2012. Duration of AEs was not reported.	No information reported.	Not Recovered/ Not Resolved	*Consumer case. Dizziness, syncope and fatigue were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]	14	[redacted]	Fatigue, Headache, Photophobia, Myalgia, Malaise, Palpitations, Nausea, Dizziness, Feeling abnormal, Chronic fatigue syndrome, Postural orthostatic tachycardia syndrome, Mast cell activation syndrome	11 days after 1st dose	Vaccinated on 14/10/2011. Onset of dizziness around 10 days after vaccination with unknown duration.	Historical Condition:Malaise, Viral infection, Blood iron decreased, Rhinitis	Unknown	*Consumer case. Fatigue and dizziness were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	*Company Comments*	Case categories
[redacted]	13	[redacted]	Post vaccination syndrome, Postural orthostatic tachycardia syndrome, Arthritis, Abdominal pain lower, Dizziness, Malaise, Hypersomnia, Dysmenorrhoea, Arthralgia, Pollakiuria, Pruritus, Nail discolouration, Head discomfort, Hearing impaired, Disturbance in attention	11 months after 3rd dose	3 doses received (17/08/2011, 29/09/2011, 16/02/2012); Postural orthostatic tachycardia syndrome lasted for 856 days.	No information reported.	Unknown	*Dizziness and disturbance in attention were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]	14	[redacted]	Urticaria, Syncope, Seizure, Pruritus, Depressed level of consciousness, Muscle spasms, Pulse absent, Erythema, Rash, Postural orthostatic tachycardia syndrome, Epileptic aura	Within 1 week after 3rd dose	Complete dates of vaccinations were not reported. Duration of AEs was not reported.	Historical Drug:CERVARIX	Not Recovered/ Not Resolved	*Syncope and depressed level of consciousness was reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
[redacted]		[redacted]	Muscular weakness, Pain in extremity, Monoparesis, Tremor, Gait disturbance, Complex regional pain syndrome	Not reported.	Date of vaccination & duration of AEs were not reported.	Not reported	unknown	*Case does not fulfil CRPS criteria based on reported events. Literature case. No description of pain was reported. It was reported that symptoms were disabling.*	Unconfirmed case
[redacted]		[redacted]	Headache, Malaise, Muscular weakness, Somnolence, Dizziness postural, Pain, Learning disorder, Hypersomnia, School refusal, Orthostatic hypotension, Postural orthostatic tachycardia syndrome, Complex regional pain syndrome, Neurofibromatosis, Single photon emission computerised tomogram abnormal, Autonomic neuropathy, Mental impairment	-	-	-	-	*Pending for LOC confirmation.*	Undassifiable

2. Analysis of cases that included signs and symptoms of POTS (suspected cases of POTS)

The following methodology was conducted to retrieve cases reporting signs and symptoms of POTS to determine potential undiagnosed or unrecognized cases in the GSK global safety database according to the case definition based on Raj 2013, and Sheldon 2015, as described above.

Table 3 presents possible symptoms of POTS matched to the MedDRA PTs grouped into eight.

Table 3: Groups of MedDRA Preferred Terms (PTs) for symptoms of POTS

Groups	MedDRA PTs
Group A	Palpitations, tremor, heart rate increased, tachycardia, tachyarrhythmia
Group B	Dizziness, dizziness exertional, dizziness postural, exercise tolerance decreased, muscular weakness, fatigue
Group C	Syncope, presyncope, loss of consciousness
Group D	Orthostatic intolerance, orthostatic heart rate response increased
Group E	Paraesthesia, sensory disturbance, blurred vision
Group F	Hyperhidrosis,
Group G	Memory impairment, disturbance in attention, confusional state, cognitive disorder,
Group H	Autonomic nervous system imbalance, urinary retention, constipation, diarrhea

To identify and determine suspected cases of POTS, 6 queries in the GSK global data base were run using the logic as presented below to explore different combination of the symptoms.

Query #1	Group A **AND** Group B **AND** Group C **AND** Group D **AND** Group E **AND** Group F **AND** Group G **AND** Group H
Query #2	Group A **AND** Group B **AND** Group D **AND** Group F
Query #3	Group A **AND** Group B **AND** Group D **AND** Group E
Query #4	Group C **AND** Group E **AND** Group F
Query #5	Group C **AND** Group D **AND** Group E **AND** Group F
Query #6	Group C **AND** Group D **AND** Group E **AND** Group H

As a result of these queries, 7 potential cases were identified and further evaluated. Five cases were reported with other concurrent conditions: epilepsy (2 cases), syncope/vasovagal syncope (2 cases), viral encephalitis (1 case). One consumer case, reported episodes of syncope which started 0 days after 3rd dose with a final diagnosis of early menopause, that resolved meanwhile, did not report data on BP, pulse and Tilt test.

One case, that also contains the MedDRA PT of POTS, was considered as unconfirmed case as Tilt test resulted in no abnormal findings.

No cases of POTS were identified in this analysis.

Altogether, using different search methodologies to retrieve all case reports indicative of POTS in the GSK global safety database for Cervarix (total N = > 24,000 spontaneous and literature reports) and following over 57 million doses of Cervarix distributed globally, five case reports fulfilled the criteria of POTS according to the established case definition (Raj 2013 and Sheldon 2015). A broader search strategy using more sensitive but less specific event terms in order to identify suspected cases of POTS did not identify additional cases in this analysis.

In conclusion, it is GSK's opinion that the outcome of this analysis is not sufficient to establish a causal association between POTS and vaccination with Cervarix. POTS will remain under close safety surveillance through routine pharmacovigilance and will be considered for evaluation as adverse events of interest in each PSUR/PBRER cycle, including development of a targeted follow-up questionnaire.

Assessor's comments

Case definition

The MAH proposed a case definition in line with Raj and Sheldon publications.

The fulfilment of point (4) of the case definition is certainly the most difficult to assess. The list of conditions to exclude should be more extended, including cardiac causes of inappropriate tachycardia, endocrine causes of hyperadrenergism, or other known causes of dysautonomia. Deficit in vitamin B12 may be associated to POTS. A special attention should be paid to the exclusion of infectious triggers other than HPV vaccination such as viral infections. In a review of a series of 152 patients conducted at the Mayo clinic in 1993-2003 (i.e. before HPV vaccination), 90.5% of patients reports suggested an antecedent of viral infection (*Thieben et al. 2007*). In a literature search of PubMed for articles published from 1990 to 2012, Benarroch found that up to 50% of cases have antecedent of viral illness (*Benarroch 2012*).

To note that POTS may also occur during pregnancy or after major surgery (*Raj 2013*).

Review of the 5 cases classified as confirmed by the company

According to the case definition (Table 1), the company selected 5 cases as confirmed POTS. The CIOMs of those 5 cases were reviewed for the fulfilment of the 4 diagnostic criteria (Table 4) and a

short description has been provided below. The assessor classified 2 of the 5 cases as POTS, 1 case as possible POTS, and two cases as unlikely (due to the lack of symptoms). A former viral infection is reported absent in only one case (case 4).

Table 4: Synthetic overview of the fulfilment of diagnosis criteria for 5 cases selected as confirmed.

POTS diagnostic criteria**	**Cases**				
	1	**2**	**3**	**4**	**5**
(1) symptoms	Not	Yes	Yes	Yes	tremor
(2) Orthostatic tachycardia*	Yes	Yes	Yes	Yes	Yes
(3) ≥6 months	Yes	Yes	Yes	unk	unk
(4) other associated disorder	unk	unk	Autonomic disfunction	unk	CRPS I
- viral infection	unk	unk	1st diagnose by GP	Not	unk
- Autoimmune disorder	-	-	Encephalitis Mastocytosis	-	-
Assessor's classification	**Not**	**POTS**	**POTS**	**Possible**	**Not**

* : orthostatic tachycardia demonstrated by tilt table test or Schellong test
** : unk = unknown

Case 1 (CIOMS [redacted]): Pain dominates the clinical picture in this report, with paroxysmal pain in the extremity 5 months after the second dose of Cervarix and chronic pain starting one week after the third dose. Typical symptoms of POTS are not described. Finger plethysmogram confirmed peripheral neuropathy.

Case 2 (CIOMS [redacted]): The medical history included self-injury, stress and school related anxiety. Stress does not exclude POTS but may favor the development of the syndrome. Peripheral neuropathy is diagnosed with no other indication of diagnostic test.

Case 3 (CIOMS [redacted]: Symptoms started 2 days after the 1st vaccination. There is evidence of re-challenge after the 2nd vaccination. Other diagnosis of interest include: 1) NMDA encephalitis with positive anti-NMDA receptor antibodies (possibly associated with immune-mediated post-vaccination reaction), 2) Mast cell activation (Some patients with POTS have mast cell activation (Raj, 2013)). A viral infection was not excluded and this was the early diagnostic from the general practitioner. Time of vaccination remains unclear.

Case 4 [redacted]): This case was reported in the literature. It is a poor documented case: time of vaccination, time of onset, history of treatment, and medical condition were not provided.

Case 5 [redacted]): This case was reported in the literature. Time of vaccination, time of onset, history of treatment, and medical condition were not provided.

Review of 13 cases classified as unconfirmed by the company

All cases reports included MedDRA PT of POTS but the diagnostic tests (tilt test table, Schoelong test) were not specified and results were not reported. In consequence, the fulfilment of the case definition cannot be assessed.

Unconfirmed cases were most frequently (8/13) reported by non health professionals. Most cases experienced chronic fatigue syndrome or myalgic encephalopathy (8/13). POTS is often a late diagnosis, sometimes confirmed several year after the beginning of the symptoms, and usually after history of chronic fatigue syndrome. In all cases, the narratives did not permit to assess if other known causes of orthostatic tachycardia were systematically excluded.

The assessor classified 3 of those cases as possible cases of POTS following HPV vaccination. The information provided in 7 cases did not permit to classify the case with a sufficient level of confidence, but POTS following vaccination cannot be ruled out. In three case, the assessor considered that the diagnose of POTS or the association of the syndrome with HPV vaccination was doubtful (Table 4)

Table 5 Summary of unconfirmed cases (based on CIOMS)

Case	POTS post-HPV vaccination	Argument from Summary of the history
6	not	Resolution within 1 week .
7	Possible	Symptoms started 5 months after 3rd dose.
8	not	Alternative diagnoses are reported: flu-like syndrome >1week, post-viral fatigue syndrome, low blood iron.
9	Unclassified	History of post-viral fatigue. Influenza-like illness <2 days (fever unspecified) following 1st dose. Symptoms started 1 days after 2nd dose but a viral episode cannot be ruled out from the narrative.
~~10~~	not	Excluded because this case (CIOMS [redacted]) is probably a duplicate of case 8 (CIOMS [redacted]): same wording of history, same batch number.
11	Unclassified	Onset of symptoms less than one month after 3rd dose. Tilt test is reported to be negative 4 years after 3rd dose.
12	Unclassified	History of post-viral fatigue. Date of vaccination unspecified. Flu-like syndrome (undescribed) 1 day after the first dose of Cervarix. Symptoms started 1 day after 2nd dose.
13	Possible	The subject was diagnosed with POTS, orthostatic hypotension and autonomic dysfunction. The subject experienced increased symptoms after the 3rd dose of Cervarix which was given by mistake. The reporter refers to multiple medical visits (including cardiology, neurology) but no details about the diagnosis of POTs are provided.
14	Unclassified	Occurrence of a one week virus-like illness (fever reported) between 1st and 2nd dose. However, symptoms were reported to increase after 2nd and 3rd dose. Dates of vaccination unknown.
15	Unclassified	Onset immediately after 1st dose. POTS was diagnosed after vaccination but the narrative is incomplete and does not allow more assessment.
16	unclassified	Other diagnoses: decreased blood iron and low grade nasal infection. However, symptoms of chronic fatigue started 11 days after the 1st dose of Cervarix. POTS was diagnosed 11 months after the vaccination, and mast cell activation syndrome was diagnosed 3,5 years after the vaccination.
17	Possible	Symptoms started 7 months after the 3rd dose of Cervarix and POTS was diagnosed (unknown test) at that time.
18	Unclassified	POTS is reported to develop within 1 month after the 3rd dose of Cervarix but the information provided is too incomplete for more assessment.

Review of 7 cases classified as potential by the company

In order to identify potential POTS in cases without MedDRA POTS PT reported, the company used an algorithm which is considered to be more specific and less sensitive. Group F 'Hyperhidrosis' does not fit to the case definition. More sensitive queries including for example "Orthostatic intolerance" AND

"one other symptom/sign" would have been preferred, although the difficulty to interpret results is well-understood.

The company selected 7 cases by using the algorithm. One case (CIOMS [redacted] actually had POTS listed among PTs and is already listed in Table 4 (case 11). The assessor agrees that the narrative of other cases do not permit to classify those cases with sufficient confidence.

Conclusion

The MAH identified 19 cases with POTS PT and 7 cases with combinations of proxy PTs. Although no level of certainty can be reached from the analysis of CIOMS, the assessor considers that two cases could likely be cases of POTS following HPV vaccination, four cases are possibly cases of POTS following HPV vaccination, and that other cases are not POTs, or possible POTS not following vaccination, or unclassifiable.

In conclusion, very few cases of POTS following HPV vaccination were identified. From data available, all conditions other than vaccination which could potentially be associated with POTS cannot be systematically excluded. However, a potential association between HPV vaccination and POTS cannot be ruled out.

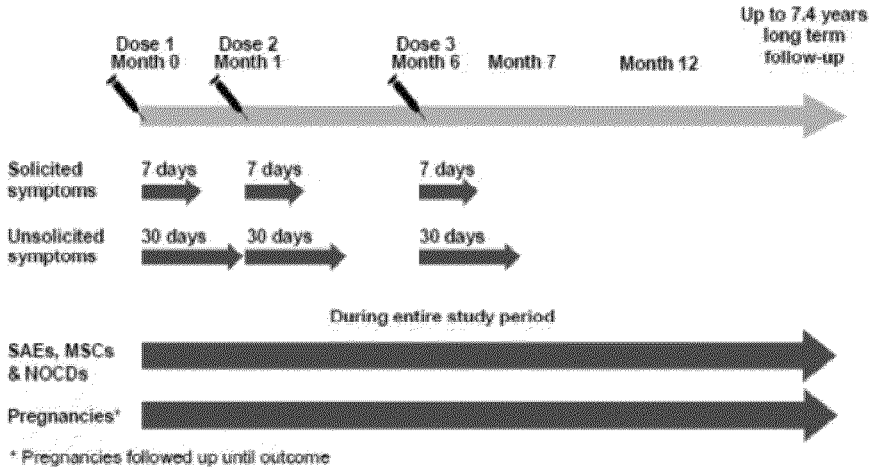
Question 2

Please provide an in depth review of cases of CRPS and POTS observed within all clinical studies; with comparison of HPV vaccine groups and control groups. If differences are observed, please discuss potential explanations including risk factors for the development of CRPS and POTS.

MAH's response

Introduction

The figure below shows an example of the safety follow-up in an HPV vaccine clinical trial.



In order to evaluate reactogenicity, diary cards are provided to record solicited local and general signs and symptoms for 7 days after each vaccination.

All 'unsolicited' symptoms reported within 30 days (day 0–29) after each dose are recorded. In most studies, medically significant conditions (MSCs), serious adverse events (SAEs), potentially immune-mediated diseases (pIMDs) are captured until study completion.

pIMDs are events either reported as such in some studies, or detected in the database by a search of MedDRA PTs related to immune-mediated diseases. A predefined list of pIMDs includes autoimmune diseases and other inflammatory disorders of interest, which may or may not have an autoimmune aetiology, including new onset of pIMD or exacerbations of pre-existing pIMDs. The list of pIMDs is thus broad, potentially including events previously classified as 'new onset of autoimmune disease' in the HPV clinical development programme.

A pooled analysis of safety data from Cervarix clinical trials including 57 580 subjects and 96 704 HPV-16/18-vaccine doses administered was published (Angelo 2014).

For the purpose of the requested analysis on CRPS and POTS, 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) were pooled together.

Three follow - up periods were considered for the analysis: within 30 days after any dose, within 6 months post last vaccination and during the entire study period. All analyses were conducted on the Total Vaccinated Cohort (TVC), which includes all subjects who received at least one dose of study vaccine, and for whom data are available. A total of 42,047 subjects (21,268 in HPV group and 20,779 in comparator groups) were included in the analysis with the Data Lock point (DLP) of 15 June 2015. The study groups were comparable for age distribution including age at the time of first vaccination.

CRPS

As discussed in response to Question 1, the company uses case definition of CRPS proposed by Harden 2010.

1. Analysis of cases that included the MedDRA Preferred Term (PT) of CRPS

No serious or non-serious adverse events that contained the MedDRA PT of CRPS were identified in the clinical trial database in this analysis.

2. Analysis of cases that included signs and symptoms of CRPS (suspected cases of CRPS)

Following the same approach as described in response to Question 1:

- a search of events that contain MedDRA PT 'Pain' or 'Pain in extremity' with duration of longer than 14 days was performed.
- Secondly, combination of events suggestive for CRPS symptoms and 'Pain' or 'Pain in extremity' were searched to determine potential undiagnosed or unrecognized cases of CRPS, refer to the Table 2. For this search it was considered that difference between the onset of Pain or Pain in extremity and onset of any of other possible symptoms of CRPS cannot be more than one month.

Table 2 Criteria established by Harden et al 2010 matched to the MedDRA Preferred Terms (PTs)

Symptoms of CRPS, Harden, 2010	MedDRA PTs
Pain: Continuing pain disproportionate to vaccination	Pain; Pain in extremity
Sensory: Allodynia deep pressure pain, Allodynia pain after movement, Allodynia after light touch, Hyperesthesia, Hypoesthesia, Hyperalgesia, Hypoalgesia	Allodynia, Hyperaesthesia, Hypoaesthesia, Sensory disturbance, Skin burning sensation
Vasomotor: Color change/difference, temperature difference	Skin discolouration, Skin hyperpigmentation, Skin hypopigmentation, Skin atrophy, Temperature difference of extremities, Skin warm, Skin depigmentation, Skin dystrophy
Pseudomotor /oedema: Transpiration disturbance, Edema	Oedema, Oedema peripheral, Hyperhidrosis, Hypohydrosis, Cold sweat, Skin oedema
Trophic: Hair growth change, Nail growth change, Trophic skin disturbance	Hair growth abnormal, Nail growth abnormal, Onychoclasis
Motor: limitation of movement, Limitation of strength, Dystonia, Tremor, Bradykinesia	Injection site movement impairment, injected limb mobility decreased, Muscular weakness, Dystonia, Tremor, Bradykinesia, Motor dysfunction

Results

The reporting frequencies of these events were similar between the groups that received HPV and control/comparator vaccines, resulting in RRs below 1.8 with 95% Confidence intervals including 1 in each of the analyses performed.

As a result of six queries described above, no subjects were reported with a combination of symptoms suggestive of POTS.

Overall, no suspected cases of POTS have been identified in this analysis. There was no evidence for a significant difference between groups for any of the follow-up periods evaluated (30 days after vaccination, 6 months after vaccination or for the entire duration of the study), with relative risks ≤ 1.80 and 95% Confidence intervals including 1 in each of the analyses performed.

In conclusion based on this analysis, there was no evidence of differences between the study groups in the reporting rates for adverse events suggestive of CRPS or POTS.

Assessor's comments

The MAH has pooled the safety data from 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups) (DLP of 15 June 2015).

The analysis of available data **did not identify any serious or non-serious adverse event of CRPS**, which contained the MedDRA PT of CRPS or which included signs and symptoms of CRPS, as according to *Harden et al. (2010)*.

POTS

As discussed in response to Question 1, the company uses case definition of POTS based on Raj et al, 2013 and Sheldon et al, 2015.

1. Analysis of cases that included the MedDRA Preferred Term (PT) of POTS

No serious or non-serious events that contained the MedDRA PT of POTS were identified in the clinical trial database in this analysis.

2. Analysis of cases that included signs and symptoms of POTS (suspected cases of POTS)

A search for suspected cases of POTS was performed similarly to what was described in response to Question1.

Possible symptoms of POTS were matched to the MedDRA PTs which were grouped in eight as described in Table 5.

Table 6: Groups of MedDRA Preferred Terms (PTs) for symptoms of POTS.

Groups	MedDRA PTs
Group A	Palpitations, tremor, heart rate increased, tachycardia, tachyarrhythmia
Group B	Dizziness, dizziness exertional, dizziness postural, exercise tolerance decreased, muscular weakness, fatigue
Group C	Syncope, presyncope, loss of consciousness
Group D	Orthostatic intolerance, orthostatic heart rate response increased
Group E	Paraesthesia, sensory disturbance, blurred vision
Group F	Hyperhidrosis,
Group G	Memory impairment, disturbance in attention, confusional state, cognitive disorder,
Group H	Autonomic nervous system imbalance, urinary retention, constipation, diarrhea

To identify and determine suspected cases of POTS, 6 queries were run using the logic as presented below to explore different combination of the symptoms.

Query #1	Group A **AND** Group B **AND** Group C **AND** Group D **AND** Group E **AND** Group F **AND** Group G **AND** Group H
Query #2	Group A **AND** Group B **AND** Group D **AND** Group F
Query #3	Group A **AND** Group B **AND** Group D **AND** Group E
Query #4	Group C **AND** Group E **AND** Group F
Query #5	Group C **AND** Group D **AND** Group E **AND** Group F
Query #6	Group C **AND** Group D **AND** Group E **AND** Group H

Again, the onset of symptoms should not be more than 1 month as compared to group A for categories 1, 2, 3 and not more than 1 month as compared to group C for categories 4, 5, 6.

Results

The reporting frequencies of these events were similar between the groups that received HPV and control/comparator vaccines in each of the analyses performed within 30 days after vaccination, within 6 months after the vaccination, and during the study period.

As a result of six queries described above, no subjects were reported with a combination of symptoms suggestive of POTS.

Overall, no suspected cases of POTS have been identified in this analysis. There was no evidence for a significant difference between groups for any of the follow-up periods evaluated (30 days after vaccination, 6 months after vaccination or for the entire duration of the study), with relative risks ≤ 1.80 and 95% Confidence intervals including 1 in each of the analyses performed.

In conclusion based on this analysis, there was no evidence of differences between the study groups in the reporting rates for adverse events suggestive of CRPS or POTS.

Assessor's comments

Similarly to CRPS, **no serious nor non-serious cases of POTS** have been identified under the PT POTS, or using diagnostic criteria of POTS (*Raj 2013* and *Sheldon et al. 2015*).

Question 3

The MAHs should provide an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population, stratified by region, if available. The analysis should discuss the assumptions made with respect to the background incidence in the target population and also the influence of potential under-reporting of cases in association with HPV vaccines.

Introduction

The assessor summarized here-after the method used by the MAH to compare the observed and the expected numbers of cases of CRPS and POTS following vaccination with Cervarix (see Annnex 1 of the Responses to Questions). The MAH provided also the comprehensive review of published literature conducted by MAH and SP/MSD to derive the background incidence rates for CRPS and POTS for consideration in observed/expected analyses (see Annex 2 of the *Responses to Questions*).

CRPS

Summary of the MAH's response

- **Methods**

The MAH proposed a model to compare observed and expected number of cases of CRPS following Cervarix vaccination with:

- $Observed\ number = observed\ number\ of\ CRPS\ cases\ within\ the\ risk\ period$
- $$Expected\ number = \frac{age-adjusted\ background\ incidence\ rate}{100{,}000} \times \frac{number\ of\ doses\ sold * 0.75}{3} \times \frac{Time\ at\ risk\ per\ person\ \ (in\ weeks)}{52} \times reported\ fraction$$

The assumptions were:

- 75% (0.75) of the doses distributed are administered. This proportion was derived from the UK vaccination campaign data by comparing the number of doses distributed with the measured vaccine coverage;
- All beneficiaries received the three (3) doses of the full vaccine schedule.

The "observed" number of CRPS cases was based on the 49 spontaneous case reports from the MAH safety database (see the response to question 1 and Table 5). Five cases were classified as confirmed, 37 cases were classified as unconfirmed, 6 cases were classified as unlikely, and 1 case was considered to be unassessable.

Table 7: Number of cases and number of doses of Cervarix distributed per Region/countries (at the DLP 15 June 2015)

Country	Cervarix doses distributed (nb)	CRPS spontaneous case reports (nb)	CRPS reporting rate (per 100,000 doses)
Japan	[redacted]	[redacted]	0.57
UK			0.092
R. of Korea			0.043
Worldwide	57,094,396	49	0.086

A best-case safety scenario included only confirmed cases of CRPS, a midcase safety scenario included the confirmed and unconfirmed cases of CRPS and the worst-case safety scenario included the confirmed, the unconfirmed and the unlikely cases of CRPS. For the observed-to-expected analysis, only cases occurring in the pre-defined risk periods were considered (risk periods are defined below). In addition, cases with missing Time-To-Onset (TTO) data were added in proportion to those in the time window of interest for the mid-case safety scenario, and all of them for the worst-case safety scenario.

The analysis was performed for worldwide data, for Japan, for the UK and the Republic of Korea. The analysis was not performed for Europe as no cases were reported from other European countries than the UK.

The "expected number of cases was based on estimated background incidence rate from the Netherlands (40.4 per 100,000 person-years for females, de Mos 2007). Each age stratum was provided with an estimated weight based on the age distribution of the population exposed to the vaccine that reported an adverse event. As the actual age distribution of the exposed (vaccinated) population is not available, the age distribution across all worldwide, Japanese, British and Korean spontaneous cases identified in the global safety database for Cervarix was used as a proxy. The age-adjusted background incidence rates corresponding to vaccinated females was estimated by taking the weighted average of the incidence rates within each age stratum.

Different risk periods post exposure to a Cervarix dose were used (ranging from 1 week to 2 years), as well as different percentages of cases actually spontaneously reported among all those that occurred within the risk period (ranging between 1% and 100%).

- **Results**

The results have been summarized by the assessor in the Table below. Exact figures are not provided in the report but are extracted from the figures.

Table: Reporting fraction of CRPS observed cases (O) when O is higher or lower than the expected number of cases (E) according safety scenarios, for a risk period of 1 week.

	Best case	**Mid case**	**Worst case**
Worldwide			
O > E	≤2%	≤15%	≤23%
O > E significantly	never	≤~9%	≤~16%
Japan			
O > E	≤12%	≤71%	any
O > E significantly	≤~1%	≤~35%	≤~99%
United Kingdom			
O > E	≤10%	≤36%	≤42%
O > E significantly	≤~1%	≤~14%	≤~18%

For worldwide reported cases, if we consider 1 week as risk period, the number of cases observed is equal or lower than the expected number if at least 2%, 15% and 23% of the cases occurring within 1 week of Cervarix vaccination were reported in the best-, the mid- and the worst-case safety scenario, respectively. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected.

For Japan, considering a risk period after each dose of 1 week, the number of CRPS cases observed is equal or lower to the number expected if at least 12% and 71% of the cases occurring within 1 week of Cervarix vaccination were reported in the best- and the mid-case safety scenario, respectively. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected. In a worst-case safety scenario, whatever the reported fraction, the observed number of CRPS cases is higher than expected in the risk period of 1 week post Cervarix dose. However, the worst case safety scenario included all confirmed, unconfirmed and unlikely cases of CRPS and considered all cases with unknown time to onset as having occurred within the risk period. The media attention in Japan could have generated the reporting of CRPS cases post Cervarix which would finally have been diagnosed as unconfirmed or unlikely making the worst case scenario sensitive to a media effect. Indeed, increased reporting of suspected CRPS cases in Japan coincided with extensive media coverage of a CRPS case in Japan (Wilson 2014). For longer risk periods, the observed number of cases is lower than expected for some thresholds of reported fraction.

For United Kingdom, considering a 1 week risk period (time at risk per person of 3 weeks), the number of CRPS cases observed is equal or lower than the expected if at least 10%, 36% and 42% of the cases occurring within 1 week of Cervarix vaccination were reported in the best-, the mid- and the worst-case safety scenario, respectively. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected.

For the Republic of Korea, there is only one unconfirmed case of CRPS in that country so no best-case or worst-case safety scenario is presented. This observed number of CRPS cases is equal or lower than the expected number if at least 10% of the cases occurring within 1 week of Cervarix vaccination were reported. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected.

- **Conclusions**

Considering the specificities of spontaneous reports, the longer the time between vaccination and the onset of event, the less chance it has to be reported. It means that the longer the risk period, the lower the reported fraction is. Taking a risk period of 1 week is consequently probably the most

sensitive scenario for detecting an excess of cases by using spontaneous report data. And even in that situation, for plausible values of reported fraction (10 to 70%), the observed number of cases is lower than the expected number whatever the safety scenario considered for CRPS case confirmation except for Japan in the worst case safety scenario. The media attention in Japan may have generated the reporting of CRPS cases which would finally have been diagnosed as unconfirmed or unlikely, making the worst case scenario sensitive to a media effect. Overall, the observed-to-expected analysis suggested that the observed incidence rate of CRPS following Cervarix vaccination is not significantly higher than the expected rate for a range of plausible combinations of risk periods and reporting fraction.

Assessor's comment

The Observed vs expected methodology used in this CRPS analysis is based on many assumptions, which cannot be verified. However, it is acknowledged that it is probably not possible to conduct better analyses at this stage, given the wide uncertainty around the reporting fraction for observed cases.

It is assumed by the MAH that the reported fraction of CRPS cases should be about 10 to 70%. However, adverse events have been shown to be reported at a much lower rate, i.e. from less than 1% to 10% depending of the authors (*Agarwal et al. 2013*, *Gavaza et al. 2011*, *Mirbaha et al. 2015*). Moreover, because of the difficulty of diagnosing CRPS, many patients could be undiagnosed. Therefore, the reporting rate for CRPS might be much lower than those observed for other adverse events.

The CRPS case reported by Korea relates to a woman aged 60 years and should be considered as an outlier. To note that Korean recommendations target females aged 15-17 years with a catch-up vaccination recommended for females aged 18-26 years (*Kim et al. 2014*). This case should preferably not be considered in this analysis.

The results of the Observed vs Expected analysis suggest that the number of observed CRPS cases is low compared to those expected, except in Japan. The high number of cases observed in Japan is a concern. Even if the media attention may have increased the fraction of reported cases, a reporting fraction of 71% (which is quite high for spontaneous reporting) would imply that more cases are observed than expected in the mid-case scenario – although not with statistical significance. This high number suggests that CRPS should be under further surveillance.

Based on reported cases in Japan and UK, a reporting rate at 0.31 cases per 100,000 doses (48/15,668,109) can be estimated. When this rate is applied to the number of doses distributed worldwide, 175 cases would have been reported, would the "rest of the world" had a similar reporting pattern than those two countries. Would the reporting rate in Japan be chosen, 325 cases would have been reported.

POTS

Summary of the MAH's response

- **Methods**

The GSK global safety database contained 19 spontaneous case reports for Cervarix that included the MedDRA PT of POTS for 57 094 396 doses sold worldwide (reporting rate 0.033 per 100,000 doses distributed). Among these POTS cases, [redacted] were reported in Japan for [redacted] doses distributed (reporting rate 0.11 per 100,000 doses); [redacted] cases were reported in the United Kingdom for [redacted] doses distributed (reporting rate 0.012 per 100,000 doses) and [redacted] case was reported in the United States for [redacted] doses distributed (reporting rate 0.14 per 100,000 doses).

All cases were reviewed according to the criteria suggested by Sheldon , 2015 and Raj 2013 and defined as confirmed cases of POTS or unconfirmed cases of POTS (due to lack of information). There are no unlikely cases of POTS so no worst-case safety scenario is provided. One case from Japan could not be classified and is excluded from the analysis. A best-case safety scenario for Cervarix vaccine included only confirmed cases of POTS and a mid-case safety scenario included the confirmed and unconfirmed cases of POTS.

For the observed-to-expected analysis, only cases occurring in the pre-defined risk periods were considered. In addition, cases with missing time-to-onset (TTO) data were added in proportion to those in the time window of interest for the mid-case safety scenario.

The analysis was performed for worldwide data, for Japan, for the UK and the US. The analysis was not performed for Europe as no cases were reported from other European countries than the UK.

As for the observed-to-expected analysis for CRPS, we considered that on average 75% of doses distributed/sold are administered. For all countries and region we made the assumption that all vaccinated persons received 3 doses of the vaccine.

In the observed-to-expected analysis for POTS, several risk periods post Cervarix dose were assessed: 1 week, 1 month, 6 months and 1 year (the 1 year includes the longest TTO for POTS cases reported in GSK global safety database).

There are no POTS incidence rates published in the literature so Chronic Fatigue Syndrome (CFS) incidence rates were used to give indirect estimates. Donegan provided an estimated background incidence rate of CFS among adolescent girls of 30 per 100,000 person-years in the UK and Bakken et al. provided an estimate of 70 per 100,000 person-years in Norway. The percentage of CFS cases presenting with POTS was reported by Reynolds et al. as being of 10% and by Galland et al. as being of 40%. The percentage of POTS cases presenting with CFS was reported by McDonald et al. as being of 20%. Based on these values, 4 scenarios were considered for the background incidence rate as stated in the table below.

A similar analysis as for CRPS assumed different magnitudes of reporting fraction.

Table 8 **Different scenarios for the estimation of the POTS background Incidence Rates (IR)**

	Assumption 1	Assumption 2	Assumption 3	Assumption 4
Incidence of CFS (100,000py)	30	70	30	70
%CFS cases with POTS	10	10	40	40
%POTS cases with CFS	20	20	20	20
Incidence of POTS (/100,000py)	**15**	**35**	**60**	**140**

- **Results**

For worldwide analyses, looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS worldwide and a risk period of 1 week, the observed reporting rate is equal or lower than the expected if at least 2% of the POTS cases occurring within 1 week of Cervarix

vaccination were reported for the best-case safety scenario and at least 7% of the POTS cases occurring within 1 week of Cervarix vaccination were reported for the mid-case safety scenario (Table 9Table 8). For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected. The results for other risk periods are described in the table below, and the reporting fraction is even lower.

In United Kingdom, there is no case with a TTO longer than 6 months. No confirmed cases have a TTO longer than 1 month and no best case scenario is thus presented (Table 9: **Reporting fraction of POTS observed cases (O) when O is higher than the expected number of cases (E) according safety scenarios, for the worst assumption for background rate and for different risk periods.**Table 9).

Table 9: **Reporting fraction of POTS observed cases (O) when O is higher than the expected number of cases (E) according safety scenarios, for the worst assumption for background rate and for different risk periods.**

Risk period	Best case	Mid case
Worldwide		
One week	≤2%	≤7%
One month	≤1%	≤3%
6 months	≤1%	<1%
1 year	<0.6%	≤0.6%
Japan		
One week	≤13%	≤20%
One month	≤6%	≤8%
6 months	<2%	≤2%
1 year	<1%	≤1%
United Kingdom		
One week	≤5%	≤27%
One month	No confirmed case	≤11%
6 months	No confirmed case	≤2%
United States		
One week	No confirmed case	≤65%

In the US, there are no confirmed cases, so no best case safety scenario is presented. There are no cases with a TTO beyond 1 week so no figures are presented for the risk periods beyond 1 week.

For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

- **Conclusions**

Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS and a risk period of 1 week whatever the region or safety scenario for case confirmation, the observed reporting rate of POTS is lower than the expected for plausible ranges of reported fraction (5 to 65%). For other assumptions and risk periods, the reported fraction can be even lower and still allow an observed reporting rate of POTS lower than the expected.

The observed-to-expected analysis suggested that the observed incidence rate of POTS following Cervarix vaccination is not significantly higher than the expected rate for a range of plausible combinations of incidence rates and reporting fraction.

Assessor's comments

The Observed vs Expected methodology used in this analysis is also based on many assumptions, which cannot be verified. However, as for CRPS it is probably impossible to conduct better analyses at this stage, given the wide uncertainty around the reporting fraction for observed cases and around the background rates. The analyses presented are based on the worst case scenario for background incidence rate.

The results of the Observed vs Expected analysis suggest that the number of observed POTS cases is low compared to those expected, even in Japan.

Question 4

The MAHs should provide a critical appraisal of the strength of evidence for a causal association with HPV vaccine for CRPS and POTS. This should consider the available published literature, including epidemiological studies, and also the possible causes and pathophysiology of CRPS and OTS and discuss whether there is biological basis for a possible causal association.

MAH's response

CRPS

Complex regional pain syndrome is a chronic pain disorder that typically develops in anextremity after (minor) tissue trauma (De Mos 2009; Huygen 2015; Harden 2010). Several reports have been published describing cases of CRPS occurring in adolescent girls with symptoms occurring after vaccination with human papilloma virus (HPV) vaccines (Kinoshita 2014; Richards 2012), raising questions on potential causal links that led to temporary suspension of the recommendation for HPV vaccination in Japan.

This potential safety issue was investigated by GSK and the results of an expert consultation were published (Huygen 2015). From this it was concluded that there is, at this time, not enough evidence to suggest that Cervarix causes CRPS.

A deeper analysis of the potential mechanisms behind CRPS, based on extensive literature review, considered several potential explanations that could have an impact on responses to minor trauma (De Mos 2009):

- Autonomic nervous system dysfunction
- Somatic nervous system dysfunction
- Inflammation
- Hypoxia
- Psychological factors

The potential role of inflammation is of most interest when considering any involvement of the immune system in the aetiology of CRPS. The role of inflammation was investigated by analysing artificially induced blisters (De Mos 2009). When comparing blisters from CRPS affected sites with non-affected site, increased levels of the cytokines IL-6 and TNF-α were measured as well as markers for monocyte and macrophage activation. Similarly, changes in levels of proinflammatory cytokines (IL-1β, TNF-α) in cerebrospinal fluid were detected in CRPS patients (De Mos 2009). An additional finding, supporting a role of inflammation, is the detection of enhanced migration of radio-labelled autologous leukocytes towards affected limbs (De Mos 2009). However, several standard inflammation parameters such as serum levels of C-reactive protein and white blood cell counts were normal in CRPS patients (De Mos 2009). A putative role of inflammation is consistent with reports describing successful treatment with

immune-modulating agents such as infliximab (monoclonal anti-TNF-α antibody) and thalidomide (unknown mode of action but inhibition of pro-inflammatory cytokines such as IL-6) (De Mos 2009).

Whereas a role for inflammation appears plausible, it is less clear how inflammation leads to symptoms and how inflammation could be triggered. With regards to the first question, there is evidence for cross-talk between the immune system, e.g. inflammatory responses, and the nervous system. Neurogenic inflammation can be mediated by a number of neuropeptides, such as substance P (SP), calcitonin gene-related protein (CGRP) and neuropeptide Y. Thus, a link between excessive inflammation and some neurogenic response appears possible. The second question, i.e., the trigger of the kind of inflammation that could lead to the cascade of events ultimately resulting in CRPS, is considerably less clear. It is of interest that often some sort of trauma appears to be an initiating event for CRPS. Case studies describe a variety of events as potential initiating trauma, such as wrist fractures, cancer, infections and cardiovascular events (De Mos 2009). Among antecedent infections, a variety of pathogens have been implicated (e.g., Severity of the trauma is not related to risk of CRPS. From this, it was hypothesized that symptoms occur as the result of an exaggerated neuro-inflammatory response to injury (De Mos 2009). If that is the case, then some genetic predisposition seems plausible. Indeed, polymorphisms in the TNF-α promoter, angiotensin converting enzyme and HLA genes have been described as being associated with CRPS (De Mos 2009).

The wide variety of stimuli or triggering events suggests that a single, auto-immune or antigenic mimicry cause is unlikely. Given the wide variety of triggering events, it has in fact been suggested that, in the case of vaccination, the injection event itself in susceptible persons, rather than the specific antigen, could be a triggering event (Huygen 2015). In that setting, it was considered of interest that the subcutaneous route of injection often used for vaccination in Japan could generate innate immune responses in the vicinity of skin nerves.

POTS

Postural orthostatic tachycardia syndrome is a complex disorder that is primarily characterized by an excessive increase in heart rate upon standing up (Freeman 2011). The aetiology of POTS is unknown, although the syndrome appears to be associated with conditions such as recent viral illness, chronic fatigue syndrome and a limited autonomic neuropathy (Freeman 2011). Several recent reports describe onset of POTS symptoms following vaccination with HPV vaccines (Blitshteyn 2014; Brinth 2015). Patients are predominantly female, of childbearing age, and often characterized by high levels of physical activity and irregular menstruation (Blitshteyn 2014). Of note, the number of cases that were described is small (6 and 35, respectively, in the two publications, Blitshteyn 2014; Brinth 2015). Clearly any temporal association with vaccination does not necessarily translate into causality. In fact, another study (Lin 2014) identified daily water intake, supine heart rate and sleeping hours as potential risk factors for POTS.

Mechanistically, and given that the excessive increase in heart rate is the main finding, there has been an interest in studying changes in the α/ß-adrenergic receptor system as well as levels of circulating catecholamines and norepinephrine in patients (Li 2014). This approach, combined with the observation of antecedent viral illness, has led to a hypothesis of potential auto-immune origin of POTS, focussing on detection of auto-antibodies. A single publication reported the presence of auto-antibodies against the α1-adrenergic receptor (α1AR) in patients (Li 2014). These antibodies were functional in different in vitro assays and the functional activity measured in these assays could be blocked by the α1AR antagonist prazosin (Li 2014). The proposed mode of action of such α1AR-targeted antagonistic antibodies is that the change in blood pressure following change in posture is insufficiently compensated by α1AR-mediated vasoconstriction and that this results in an exaggerated sympatho-neural response to low blood pressure (Li 2014). This 'overshoot' response could then lead to tachycardia (Li 2014).

Whereas this hypothesis is of interest and could explain the symptoms, it remains to be confirmed. The presence of anti-cardiac lipid raft proteins (Wang 2013) may provide some support for this hypothesis that auto-antibodies may play a role. Auto-antibodies against a number of proteins, including proteins associated with caveolae structure, adrenergic signalling, calcium signalling, cytostructures, chaperone and energy metabolism were identified (Wang 2013). Moreover, it has been shown that 14% of patients with POTS had antibodies against the ganglionic acetylcholine receptor (Thieben 2007).

Finally, it has been proposed that anti-phospholipid antibodies could play a role, as described for antiphospholipid (Hughes) syndrome (APS) (Schofield 2014). As the authors of that paper state, a link between POTS and APS has not previously been described, and therefore they performed a clinical evaluation of patients diagnosed with APS and an autonomic disorder, e.g., POTS (Schofield 2014). Although the authors indicate that APS and autonomic disorder symptoms can occur together (Schofield 2014), their report does not shed any new light on the proposed autoimmune aetiology. Similarly, a single study describes occurrence of POTS in multiple sclerosis (MS) patients and reports some differences in, amongst others, norepinephrine levels between POTS patients with concomitant MS or not (Adamec 2013). Whereas the authors conclude from these data that POTS is associated with MS, it must be emphasized that the numbers of patients are small, that there is no evidence for causality and that these observations could represent an epiphenomenon. Thus, it seems premature to consider the data suggesting associations with immune-mediated disorders such as APS and MS (Adamec 2013; Schofield 2014) as evidence or r indication of an auto-immune aetiology of POTS. Nevertheless, a recent analysis of 100 patients diagnosed with POTS (Blitshteyn 2015) focussing on anti-nuclear antibodies, other markers of auto-immunity and co-morbid auto-immune disorders concluded that patients with POTS have a higher prevalence of auto-immune markers and co-morbidities. 25% of patients had anti-nuclear antibodies and 20% had any form of auto-immune co-morbidity (Blitshteyn 2015), leading to a conclusion that there could either be a link between auto-immune disorders and POTS or that POTS itself could be an auto-immune disorder. An acknowledged limitation of the study is the statistical drawback of comparing prevalence of auto-immune disorders and –markers in a predominantly female POTS patient population to the prevalence in the general population (Blitshteyn 2015). The strength of the study is the relatively large cohort that was evaluated.

The complex nature of both CRPS and POTS and the facts that both conditions received attention linked to HPV vaccination and have some common symptoms, has led to a hypothesis that both disorders could be part of a spectrum of small-fibre neuropathy and dysautonomia disorders (Martinez-Lavin 2015). In brief, the author argues that common symptoms can be explained by assuming that post-vaccination immune responses trigger small-fiber neuropathy, defined by its clinical features of painful paraesthesias and autonomic dysfunction (Martinez- Lavin 2015). A criticism of this analysis is that it is solely based on the occurrence of common symptoms and that it does not propose any plausible mechanism that could link such symptoms with HPV vaccination (Martinez-Lavin 2015). The alternative hypothesis is that these are in fact different disorders with different aetiology, that share some of the downstream pathogenic pathways linked to sympathic dysfunction. Nevertheless, what can be concluded based on the available data is that some auto-immune aetiology, characterized by either auto-immune antibodies or co-morbidities cannot be excluded. However, the wide variety of auto-immune antibodies that are identified preclude concluding on any specific single mechanism. This may be consistent with the complexity of the condition itself.

Conclusion

Overall, it is concluded that there is not sufficient evidence to consider CRPS and POTS as two variants of a single spectrum of disorders. In terms of mechanisms, the most convincing explanation for CRPS points towards exaggerated responses to minor trauma whereas for POTS a role of a variety of auto-

antibodies cannot be excluded. A link with HPV vaccination is not obvious in either situation given the diversity of symptoms and proposed causative mechanisms.

In the case of CRPS, a role of the method of needle injection itself cannot be excluded.

Assessor's comments

CRPS

It appears that CRPS is caused by a **multifactorial process** involving both peripheral and central mechanisms. Potential mechanisms include nerve injury, ischemic reperfusion injury or oxidative stress, central sensitization, peripheral sensitization, altered sympathetic nervous system function or sympatho-afferent coupling, inflammatory and immune related factors, brain changes, genetic factors, psychological factors and disuse *(Bruehl 2015)*. Little is known how these mechanisms might interact. Given the diversity of presentations seen in CRPS, the relative contributions of different mechanisms probably differ across individual patients and even within patients over time *(Bruehl 2015)*. The heterogeneity in the constellations of signs and symptoms in individuals and the great variability in the response to specific treatments suggest the existence of distinct **subgroups** with different underlying pathophysiological mechanisms *(Borchers & Gerschwin 2014)*.

The **events that precipitate CRPS** most commonly are fractures, sprains, and surgery, but also include injections, local infections, burns, frostbites, even pregnancy, as well as stroke or myocardial infarction *(Borchers & Gerschwin 2014)*. The exact nature and combination of symptoms and their severity are not related to the severity of trauma, and more than 10% of patients may not recall any precipitating event *(Borchers & Gerschwin 2014*). Although it is often thought that CRPS is of psychogenic nature, there is no convincing evidence to support this hypothesis and different studies have resulted in conflicting outcomes *(Borchers & Gerschwin 2014)*.

Potential risk factors for the onset of CRPS 1 were found to include being **female, particularly postmenopausal female, ankle dislocation or intra-articular fracture, immobilisation, and a report of higher than usual levels of pain in the early phases of trauma.** It is not possible to draw definite conclusions as this evidence is heterogeneous and of mixed quality, relevance, and weighting strength against bias and has not been confirmed across multiple trials or in homogenous studies *(Pons et al. 2015)*. It has been suggested that CRPS is rare in people of non-European ancestry both in adults and children, but actual data on this issue are lacking *(Borchers & Gerschwin 2014)*.

CRPS can occur at any age, but is **relatively rare in childhood and adolescence**, with paediatric patients constituting <10% of CRPS patients seen at tertiary centres. Mean or median age at onset varies from ~37–52 years in population-based and cohort studies. The age group with the highest incidence is even more variable, ranging from the 4th to the 7th decade of life. Familial cases of CRPS I are characterized by a significantly younger age of onset, and this has also been observed for patients with spontaneous onset of CRPS I, i.e. without a known precipitating trauma or tissue injury. Onset of **paediatric CRPS** occurs most frequently in **early adolescence (peak age of onset is around 12-13 years of age)**, with the lower end of the range usually being 7 to 9 years *(Borchers & Gerschwin 2014; Borucki & Greco 2015)*. CRPS is rarely seen in young children before the age of 6 *(Borucki & Greco 2015)*.

Paediatric CRPS is mostly seen in **girls**. Often **minor trauma** is the inciting event such as a minor sprain or twist. Unlike adult patients, **lower extremity** involvement is more common by a ratio of 6:1 in paediatric patients. *(Borucki & Greco 2015)*. The affected lower limb is more often blue and colder than the healthy side and frequently shows hypoperfusion in three-phase bone scintigraphy. While primarily cold CRPS is a poor prognosticator in adults, the majority of pediatric patients achieve improvement or symptom resolution mainly with PT and cognitive–behavioural interventions, even if

relapses are common *(Borchers & Gerschwin 2014).* This is in contrast to a longitudinal study of patients (n=42) diagnosed as having CRPS in childhood found that on follow-up in adulthood an average of 12 years later, 52% still experienced pain, with 36% having documented recurrences of CRPS.179 This suggests that in many cases of childhood CRPS there may be no sustained recovery (*Bruehl 2015).*

In contrast, adults more often have involvement of an upper extremity, which initially is red and warmer than the healthy side, and only later may become cold and bluish and which shows hyperperfusion. In addition, RSD/CRPS appears to become chronic and resistant to any therapy more often in adults. **This raises the question of whether paediatric CRPS is a subgroup of the same disorder as in adults or a different entity entirely** *(Borchers & Gerschwin 2014).* The assumption that CRPS presents differently in children than in adults, has been questioned (*Bruehl 2015).* Two detailed detailed clinical evaluation studies (n=20; n=42) suggest that the same objective signs are seen in children and adolescents with CRPS as are seen in adults, including allodynia and hyperalgesia, edema, skin color and temperature changes, and motor changes (*Bruehl 2015).*

Case reports of **CRPS after HPV vaccination** in adolescent girls have been described in literature (*Kinoshita et al. 2014; Richards et al. 2012).* Richards et al. report one patient who was diagnosed with CRPS after vaccination with a bivalent HPV vaccine, for which the involvement of the HPV vaccine cannot be ruled out, and three patients with a quadrivalent HPV vaccine. Kinoshita et al. report 44 girls that were referred after HPV vaccination (31 received Cervarix, 13 Gardasil). In a number of girls, CRPS was diagnosed. However, the number differ depending on the use of the Japanese diagnostic criteria (4 CRPS cases) or the international diagnostic criteria (the Budapest criteria; 18 cases). It seems that there might be an error in this publication as the authors might have wrongly interpreted the Budapest criteria. It is very unlikely that the Budapest criteria would result in more confirmed diagnoses than the Japanese criteria, as the Budapest criteria are more specific.

It is hypothesized that intramuscular immunization is a sufficient painful stimulus to trigger the development of CRPS-1, and that is the **process of a needle penetrating the skin** that is the trigger, rather than a particular vaccine antigen or adjuvant being causally related *(Richards et al. 2012)*. This is supported by reports of CRPS following other needle-based interventions, including **venipuncture, intravenous drug administration** and **other vaccinations** (influenza, rubella, hepatitis B and diphtheria-tetanus with or without acellular pertussis) *(Richards et al. 2012; Kwun et al. 2012; Genc et al. 2005; Jastaniah et al. 2003; Bilic et al. 2013).* However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections

Conclusion : At this moment, literature does not point out a causal relationship between HPV vaccination and the onset of CRPS, however this cannot be ruled out for the following reasons:

- the disease is probably caused by a **multifactorial process, including inflammatory and immune related factors**. Evidence of the involvement of inflammatory mechanisms, especially in the acute phase, comes from studies documenting raised concentrations of proinflammatory neuropeptides and mediators (substance P, calcitonin gene related peptide, bradykinin) and cytokines (IL-1β, IL-2, and IL-6, and tumor necrosis factor α (TNF- α) in the systemic circulation, cerebrospinal fluid, and affected limbs of patients with CRPS *(Bruehl 2015).*

- an autoimmune cause has also been suggested for CRPS in a subset of patients. For example, *Dirckx et al.* (*2015*) have found the presence of autoantibodies in 33% of CRPS patients and in 4% of controls. Furthermore, motor impairment, a characteristic of CRPS, has been observed in healthy mice when transferring IgG from CRPS patients *Goebel et al.* (*2011*).

- CRPS occurs most commonly in women between 50 and 70 years of age *(Rockett 2014)* and is **relatively rare in childhood and adolescence which is the target population of HPV vaccination** *(Borchers & Gerschwin 2014)*.

- Paediatric CRPS is mostly triggered by **minor trauma** *(Borucki & Greco 2015)*.

POTS

As Raj pointed, POTS is a syndrome, not a disease (*Raj 2013*). Although orthostatic tachycardia is the main sign of the condition, the syndrome can be associated (or not) to a variety of conditions: in many patients, elevated levels of plasma norepinephrine; in some patients, autonomic neuropathy with preferential denervation of sympathetic nerve; in rare patients, a single point mutation causing a loss of function in the norepinephrine transporter; in some patients, co-existent mast cell activation; finally, in some patients, POTS is caused by plasma volume deficit (*Raj 2013*).

When considering the possibility of POTS after HPV vaccination, two conditions are of major interest.

1) POTS as an autoimmune condition: the MAH discussed the pro- and contra- of the autoimmune theory which is supported by the identification in a significant proportion of the cases of antibodies, the report of viral infections before onset and the presence of autoimmune markers (*Blitshteyn 2015*).

2) POTS as a dysfunction of the autonomic nervous system: In a recent publication, WHO identified in Vigibase 21 cases of gastrointestinal motility disorders after HPV vaccine (*Chandler 2015*), those conditions being suspected to be caused by autonomic neuropathies. Dysfunctions of the autonomic nervous system may present under various forms. The identification of dysautonomic conditions of interest should be discussed for future surveillance.

Is there a link between CRPS and POTS?

Recently it has been hypothesized that **small fiber neuropathy** and dysautonomia could be a common underlying pathogenesis to CRPS and POTS that follow HPV vaccination, **based on clinical manifestations** of small fiber neuropathy (pain and dysautonomia) in CRPS and POTS *(Martinez-Lavin 2015; Chandler 2015)*.

Small fiber neuropathy is a disease of the most distal nociceptive and sympathetic fibers. The outstanding clinical features of small fiber neuropathy are pain paresthesias and autonomic dysfunction. Neurological examination is usually normal, as are the electromyography and clinically available nerve conduction studies. The diagnosis of small fiber neuropathy is confirmed by skin biopsy. Corneal confocal microscopy is a new method to assess small nerve fiber pathology. These objective procedures show diminished intraepidermal or corneal small fiber innervations *(Martinez-Lavin 2015)*.

Evidence for small-fiber neuropathy has been found in some patients with CRPS, and may be prevalent in paediatric patients with a variety of chronic pain syndromes *(Borucki et al. 2015)*. However, data on small-fiber degeneration come either from patients with long-standing disease severe enough to necessitate amputation, or almost exclusively from patients with chronic disease of > 2 years duration. **Therefore, it cannot be determined whether these neuropathological changes are causally involved in the development of CRPS I or arise as a consequence of other disease-associated processes**, such as tissue hypoxia or inflammation (*Borchers & Gerschwin 2014*). Furthermore, evidence supports that small fiber neuropathy **does not constitute a major pathogenetic mechanism** in CRPS I. It appears that warm and cold hypoesthesia is significantly worse in patients with chronic (> 12 months) CRPS compared to those in the more acute stages of the disorder (≤ 12 months). **This suggests that small fiber dysfunction or loss results from, rather than being the cause of, the disease process** *(Borchers & Gerschwin 2014)*.

A study of patients aged 6–21 years with a variety of widespread pain syndromes showed that **59% of patients met the diagnostic criteria for small-fiber predominant polyneuropathy** (SFPN), indicating that this disease process may be prevalent in paediatric patients with a variety of chronic pain syndromes, although additional data are needed *(Borucki & Greco 2015).*

An altered process of **inactivated HPV virus and aluminum adjuvant** that damage dorsal root ganglia could be suggested as a preliminary pathogenetic speculation for the development of small fiber neuropathy. In animal models, aluminium is able to damage dorsal root ganglia *(Martinez-Lavin 2015).*

Although pediatric CRPS patients reported multiple systemic autonomic symptoms and regional sensory, motor, and autonomic complaints at presentation, they exhibited relatively milder abnormalities in observable signs by physical examination and tilt table testing. In this respect, they appear different from both patients with POTS and from controls (*Meier et al. 2006*).

Conclusion

The proposed common underlying pathogenesis of CRPS and POTS, i.e. small fiber neuropathy and autonomic dysfunction, cannot be explained in all CRPS cases. Furthermore, more than one mechanism seem to be involved in the pathogenesis of CRPS. There are some doubts whether small fiber neuropathy results from CRPS or causes the disease. On the other hand, there is more evidence which underlies an autoimmune hypothesis for POTS.

The link between POTS and CRPS is largely unknown and it is doubtful that both syndromes should be associated if additional investigations are required. It is preferable to investigate potential associations of HPV vaccination with POTS and HPV vaccination with CRPS separately without extrapolating on hypothetical common causal patterns.

Question 5

The MAHs should discuss the need for possible risk minimization tools and provide proposals as appropriate.

MAH's response

The MAH has conducted different analysis of all available data on CRPS and POTS that have been reported to the company following vaccination with Cervarix from launch (17 May 2007) up to the data lock point of 15 June 2015, including data sources from:

- spontaneous reports in post-marketing from over 24,000 reports following over 57 million doses distributed globally,
- all serious and non-serious AEs in the overall clinical trial programme; overall N evaluated= 42,047(21,444[HPV]; 20,603 [control/comparator vaccines] and
- case reports identified in the literature

To ensure that all cases of CRPS and POTS were identified, various search methodologies to retrieve case reports from the GSK safety database were used to identify suspected cases. For CRPS, an additional search was also performed based on search criteria used by SPMSD.

In addition to the review of individual case reports according to the established case definition of CRPS and POTS (see responses provided in Question 1 and Question 2), quantitative analyses were also conducted showing observed/expected analyses based on different scenarios (reporting rate, case classification, risk period, countries, underreporting and background rates) (see response provided in

Question 3). Importantly, an appraisal of the strength of evidence was also provided to determine any biological basis for possible causal association of CRPS and POTS with HPV (Cervarix) vaccination (see response provided in Question 4).

Overall, following over 57 million doses of Cervarix distributed worldwide, five case reports fulfil the criteria of CRPS according to the established case definition. No additional confirmed cases of CRPS were identified in the global safety database considering the other broader search criteria for suspected cases. For the three suspected cases of CRPS that reported the combination of pain or pain in extremity which have been identified following the broad search criteria, the information reported for these cases was insufficient to confirm a diagnosis of CRPS. No cases of CRPS were identified in the overall clinical trial program with Cervarix and quantitative analyses did not show any indication of a potential association between Cervarix and CRPS. In terms of mechanism, the most convincing explanation for CRPS points towards exaggerated responses to minor trauma where the role of the method of needle injection itself cannot be excluded.

Given the increased reporting and heightened public concern on the safety of HPV vaccines in Japan, triggered by the case report of CRPS in Japan in 2013, GSK have since conducted comprehensive analyses with regard to CRPS including consultation with an independent expert panel for 'pain'. Following the similar methodology outlined in response to Question 1 and after the preliminary review of the identified CRPS cases by a GSK safety physician, the two independent external experts were provided with the individual clinical narratives of identified cases for review using the same case definition (Harden 2010). The assessment of cases by GSK and the results of the quantitative analyses were only shared with the experts once their own separate assessments of individual cases were completed. Results of this safety evaluation have just been published (Huygen, 2015) and are very much in line with the outcome of these investigations.

Based on current data on POTS as provided in response to Question 1, five case reports fulfilled the criteria according to the established case definition (Raj 2013 and Sheldon 2015). The broader search strategy has not identified any suspected cases of POTS.

In conclusion, the outcomes of the different analyses performed are not sufficient to establish a causal association between CRPS or POTS and vaccination with Cervarix. It is GSK's opinion that the known benefit:risk profile of Cervarix remains unchanged and that no change is warranted to the current Reference Safety Information for Cervarix as an outcome of the assessments made in these investigations.

Given the current scientific evidence available at this time, CRPS and POTS will remain under close safety surveillance through routine pharmacovigilance including the use of targeted follow up questionnaires. The questionnaire has been implemented for CRPS and is currently being used for any case report indicative of CRPS to ensure complete documentation of suspected case which will allow a robust data evaluation/validation.

Similarly as part of routine pharmacovigilance, both CRPS and POTS will be considered for evaluation as adverse events of interest in each PSUR/PBRER cycle to determine the need for additional risk minimisation measures (if any).

Assessor's comments

CRPS

The assessment of the data provided by the MAH and of the literature has shown that:

- out of 49 spontaneous reports of CRPS (i.e. PT CRPS), 5 cases have been considered as confirmed CRPS, i.e. with fulfilment of the Budapest clinical diagnostic criteria for CRPS. In 3 of these

cases, a causal relationship with Cervarix vaccination cannot be ruled out, including 1 serious case resolved with sequelae. Among the 44 remaining *potential* CRPS cases (i.e. PT CRPS reported but insufficient information or incomplete fulfilment of the diagnostic criteria), only in 8 cases, including 4 serious cases, with an unknown outcome in 50%, and recovering/resolving in the other half, the involvement of Cervarix cannot be ruled out;

- besides, 10 cases of *potential* CRPS have been identified by applying the search strategy of signs and symptoms of CRPS (cases not reporting PT CRPS). In 2 cases the involvement of Cervarix administration could not be ruled out, one of which was serious and no recovery was observed;

- no cases of CRPS have been identified during clinical trials with Cervarix;

- the number of CRPS cases following administration of Cervarix is considered low compared to 57 million doses of Cervarix distributed globally. However, the low number might be contributed by the problem of underreporting of ADRs in general, and more specific, the difficulty of diagnosing CRPS being a complex syndrome with a variety of signs and symptoms in highly variable combinations with a variable progression over time. Furthermore, there is no golden standard diagnostic test for CRPS available, remaining CRPS as a syndrome of exclusion of other diseases with similar signs and symptoms, and no overall consensus on the clinical diagnostic criteria of CRPS (*Rockett 2014*). However the most widely accepted diagnostic criteria are the Budapest criteria described by *Harden et al.* (*2010*). All taken together, many patients could be undiagnosed;

- the Observed vs expected analysis has suggested that the number of observed CRPS cases is low compared to those expected, except in Japan. Based on reported cases in Japan and UK, a reporting rate at 0.31 cases per 100,000 doses (48/15,668,109) can be estimated. When this rate is applied to the number of doses distributed worldwide, 175 cases would have been reported, assuming that the reporting pattern is similar in other countries;

- data from the literature do not point out a causal relationship between HPV vaccination and the onset of CRPS, however this cannot be ruled out for the following reasons: (i) the disease is probably caused by a multifactorial process, including inflammatory and immune related factors, (ii) CRPS occurs most commonly in women between 50 and 70 years of age *(Rockett 2014)* and is relatively rare in childhood and adolescence which is the target population of HPV vaccination (*Borchers & Gerschwin 2015*), and (iii) paediatric CRPS is mostly triggered by minor trauma.

Taken all these data together, a causal relationship between vaccination with Cervarix and the occurrence of CRPS cannot be excluded at this stage. Therefore, additional data are needed, which could also respond to the growing public attention.

This could be accomplished by further monitoring in PSUR. However, monitoring is difficult because of the complexity of the disease and the risk of underdiagnosis. On the other hand, the high number of cases observed in Japan suggests that CRPS should be under further surveillance. As also suggested by three independent external experts, a PASS study could be useful to obtain further data regarding the potential link between CRPS and Cervarix vaccination. The feasibility of such a study should be thoroughly examined as the majority of CRPS cases normally occurs in elderly women and the target population would be adolescents. A clear definition of CRPS cases should be provided before the beginning of the PASS study, as well as the risk period. In order to obtain cases, data from specialised centres could be used.

POTS

The assessment of the data provided by the MAH and of the literature has shown that:

* Very rare documented cases support the hypothesis that POTS follow a HPV vaccination;

* POTS is most common in female adolescent and female young adults. This range of ages partially overlap the range of ages for HPV vaccination. Yet, the expected occurrence of POTS in this population is unknown and it is currently not possible to demonstrate whether HPV vaccination programmes impacted the incidence of POTS.

* To the current knowledge, there is no evidence that a causal association between HPV vaccine and POTS is biologically supported. However, two hypothesis are of interest: POTS as a autoimmune disorder and POTS as a dysfunction of the autonomic nervous system.

In consequences, the assessment is based on many unknowns. The question is:

Is it useful to identify a set of relevant autonomic disorders to monitor in enhanced surveillance of HPV vaccines? (referring to gastrointestinal motility disorders identified by *Chandler 2015*).

Moreover, the assessor would recommend to:

1) to identify PTs/codes which could be associated to autonomic disorders, including POTS (assuming that the POTS PT is not sufficient to identify POTS) and to define a POTS/autonomic disorders search strategy in pharmacovigilance data bases and other data bases;

2) to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders.

Appendix B Additional data

The following additional submissions were received:

Submission by	Date
EMA	
HPV referral – literature search POTS	21/07/2015
HPV referral – literature search POTS	30/07/2015
EV data on HPV vaccines and CRPS, POTS	12/08/2015
Dr Luc Kiebooms and Dr Andre Devos	
Motivation PRAC study	17/08/2015
Danish Health and Medicines Authority	
Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines	04/09/2015

European Medicines Agency

- **HPV referral – literature search POTS**

  The EMA has performed a systematic bibliographic search regarding Postural Orthostatic Tachycardia Syndrome:

  [redacted]

  Assessor's comments

  The bibliographic references provided by the EMA have been integrated in the assessment of MAH's responses.

  Briefly:

  - Four publications that report POTS in patients who received the HPV vaccine have been identified (*Blitshteyn 2010; Blitshteyn 2014; Brinth et al. 2015; Martinez-Lavin 2015*).

  - The diagnostic criteria for POTS have been discussed (i.e. a rise in heart rate of ≥30 bpm, or a heart rate of >120 bmp, within 10 minutes of head-up tilt or standing, but without orthostatic hypotension; and for adolescents an increase in heart rate of at least 40 bpm for) (*Mathias et al. 2012; Singer et al. 2012*). A description of the most common symptoms of POTS have been provided (i.e. orthostatic intolerance with either syncope or presyncope, fatigue, light-headedness, dizziness, palpitations, visual disturbances, clamminess, nausea, headache, pain (chest or upper abdomen), shortness of breath, and non-specific symptoms such as lethargy, impaired cognitive function, difficulty concentrating (*Mathias et al. 2012*; *Schondorf et al. 1993*; *Deb. et al 2015*)

- The possible causes of POTS have also been reviewed (i.e. neuropathic POTS, hyperadrenergic POTS, volume dysregulation, and physical deconditioning) (*Benarroch 2012; Mathias et al. 2012*)

- A link between POTS and chronic fatigue syndrome (CFS) has been suggested by different authors (*Benarroch 2012*, *van Cauwenbergh et al 2014*), as well a link with small-fiber neuropathy (*Martinez-Lavin 2015*, *Haensch et al. 2014*, *Gibbons et al 2013*).

- Regarding the background incidence of POTS in the general population, no data is available to date. However, it has been suggested that the prevalence of POTS in patients with chronique fatigue syndrome could be estimated to 170 cases per 100,000 persons (*Schondorf et al 1999*).

- Data from a LAREB Report in HPV reports provided in systematic bibliographic search on CRPS have shown that no report with a diagnosis of POTS has been identified at the time of report. Besides, in the reports of side effects with combinations that match the symptoms of POTS - such as dizziness and fainting – there was no clear evidence for POTS. In six reports of fatigue where there was also fainting in combination with dizziness symptoms had not resolved at the time of reporting. Lareb will investigate these reports of prolonged fatigue and reports of (near) fainting combined with dizziness. This will include the progress and current symptoms, whether further medical examination was performed, and whether a diagnosis was made. We will also ask for symptoms that could indicate POTS.

- **HPV referral – literature search CRPS**

  The EMA has performed a systematic bibliographic search regarding Complex Regional Pain Syndrome:

  [redacted]

Assessor's comments

The bibliographic references provided by the EMA have been integrated in the assessment of MAH's responses.

Briefly:

- Two publications that report CRPS in patients who received the HPV vaccine have been identified (*Richards et al. 2012*; Kinoshita et al. 2014).

- A description of the criteria used for the CRPS diagnostic have been provided. A discussion regarding the differences between the mostly used 'Budapest criteria' and the Japanese diagnostic criteria has been provided and pointed out that using the Japanese criteria would diagnose more patients than the Budapest criteria. It has also been outlined that there is no consensus on the diagnosis of CRPS, and that the question whether CRPS is a syndrome in its own right has been raised (*Borchers & Gerschwin 2014*, *Rockett 2014*, *Kinoshita et al. 2014*).

- The EMA report discusses the possible causes suggested for CRPS (i.e. psychological factors, immobilisation, sympathetic nervous system, neurogenic inflammation and vasomotor disturbances, neuropeptides and pain, cytokines, deep-tissue microvascular pathology hypothesis, small-fiber neuropathy hypothesis, cortical reorganisation, central changes in pain

processing, genetic predisposition, and autoimmunity) (*Borchers & Gerschwin 2014*, *Dirckx et al. 2015*, *Ostergaard et al. 2014*, *Richards et al. 2012*).

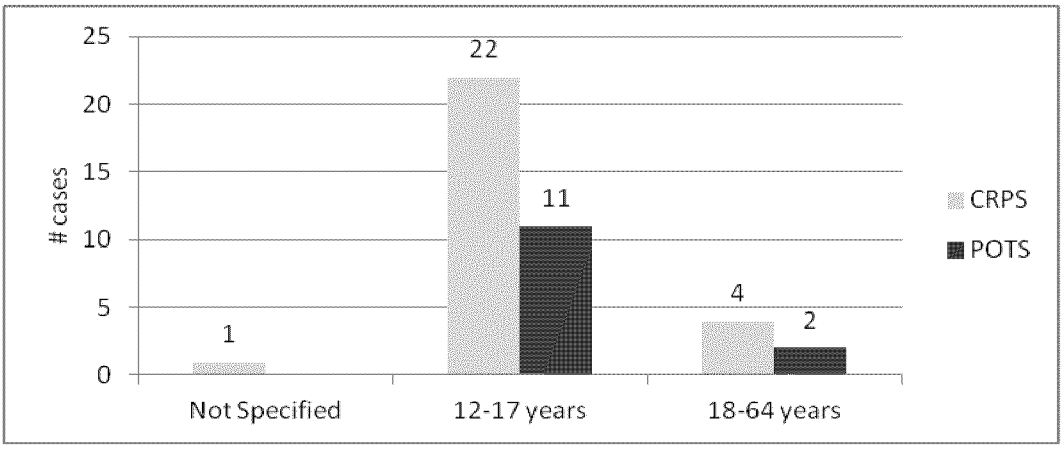
- According to *de Mos et al. 2007* and *Sandroni et al. 2003*, the background incidence rate should vary between 5.46 (US) and 26.2 (NL) per 100,000 person-years. Besides, in the target population, i.e. females 10-19 years, the incidence rate is 2.15 per 100,000 person-years in the US study and 14.9 per 100,000 person-years in the Dutch study.

- Data from a LAREB Report from HPV vaccinated patients have also been provided: Lareb received 1142 reports of suspected adverse reactions following vaccination Cervarix. Most were mild and transient. There were 48 serious reports according to international criteria. There were no reports received with a diagnosis of CRPS or POTS at the time of report. One case reported chronic pain at the injection site.

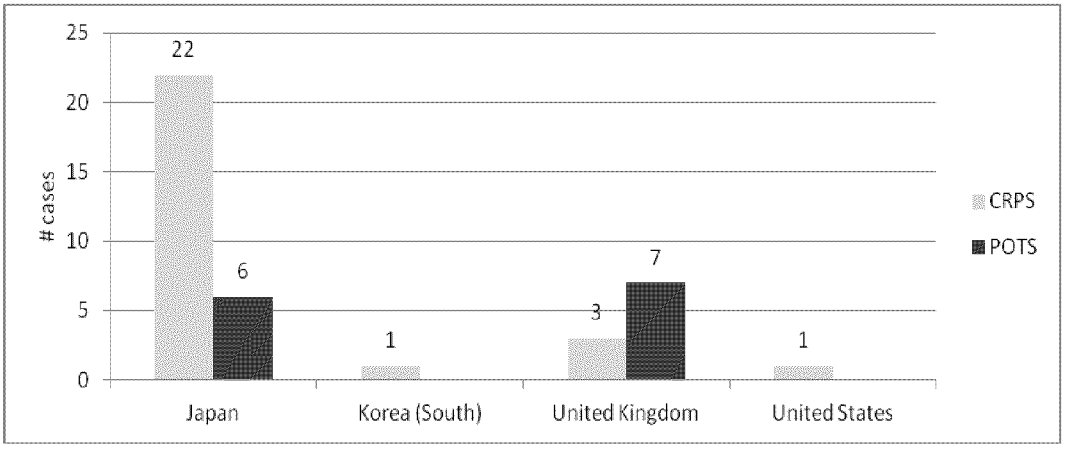
- **EVDAS search**

The EMA has performed a search in the EudraVigilance data base for cases of CRPS and POTS following vaccination with Cervarix. The obtained results are summarised below.

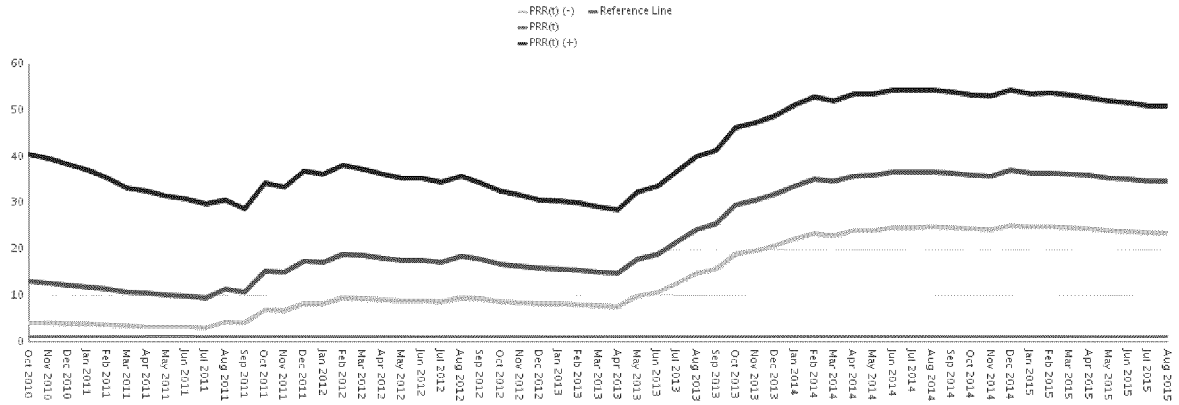
Cervarix – number of cases of CRPS (N=27) and POTS (N=13) per age range



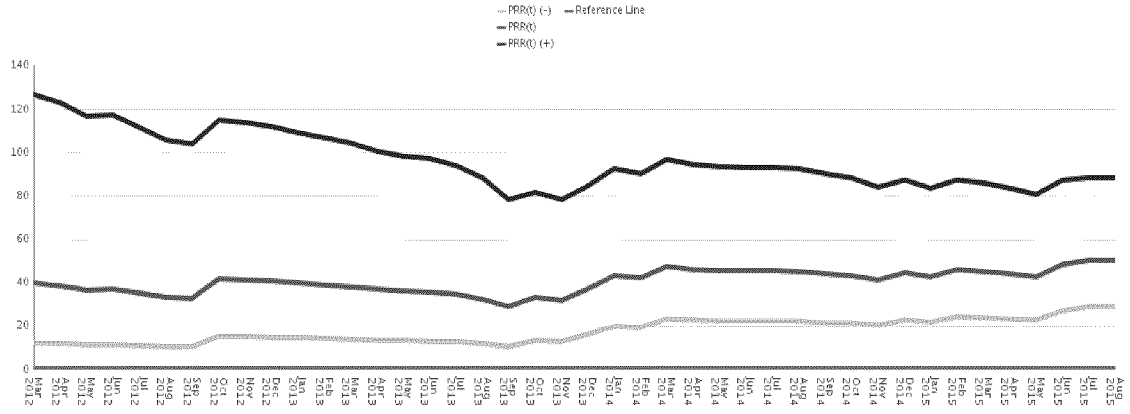
CERVARIX - number of cases of CRPS (N=27) and POTS (N=13) per occurrence country



CERVARIX - Complex Regional Pain Syndrome - dynamic PRR and cases over time



CERVARIX - Postural Orthostatic Tachycardia Syndrome - dynamic PRR and cases over time



Assessor's comments

CRPS

A total of 27 cases of CRPS have been reported in the EudraVigilance database, mainly in girls between 12 and 17 years old (81%), who belong to the target population for HPV vaccination. Most of the cases have occurred in Japan, and an increase in the number of reported cases has been observed in 2013. These two observations may be explained by the initial concerns regarding HPV vaccination and CRPS that originate in Japan and have led the Japanese authorities to suspend their active recommendation for HPV-vaccination.

Of note, according to EVDAS, a case has occur in the US. This case was not included in the cumulative review provided by the MAH. This case relates to a 13-years-old girl who reported several adverse events following vaccination with Cervarix, Menveo, Boostrix, and Varivax (reported PTs for the case are complex regional pain syndrome, fibromyalgia, hypoaesthesia, local swelling, pain, pain in extremity, and tremor). Her medical history included asthma, tonsillectomy, Helicobacter pylori infection, allergic rhinitis and lactose intolerance. As this case was confounded by other vaccines and poorly documented, it was not included in the assessment of CRPS cases (cfr question 1).

POTS

A total of 13 cases of CRPS have been reported in the EudraVigilance database, mainly in girls between 12 and 17 years old (84%). Cases have occurred in Japan and UK. The reporting rate seems quite stable over the time.

Dr Luc Kiebooms and Dr Andre Devos

- **Motivation PRAC study**

Summary

More than 1000 spontaneous reports in Denmark, of which 283 seriously, are the occasion of a review by the PRAC[1]. This concerns a complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). Are the 283/500.000 serious side effects sufficient to put vaccination into question?

The EMA uses exclusively the reporting, which has amounted to a large number of cases. But reporting is a particularly weak method to evaluate the side effects.

The Vioxx scandal[2] and Diane-35-problems have shown how weak reporting is. In both cases there has been reporting for years, but this was done with the same methodology as suggested here. So the insight into the actual extent and severity of the phenomenon was slowed down tremendously. In both cases afterwards it turned out, that the makers of the medicine knew of the adverse reactions, before the medication was brought into circulation.

For HPV now, the same seems to occur. We are at the stage of a reporting of a particularly large number of cases for a vaccination, for which a zero tolerance regarding the side effects should prevail[3]. Until now all the literature is exclusively under the direct supervision of the industry, probably even all information comes from the industry. There are no independent studies, despite the fact that these were raised on several levels (see below).

We ask from now a fully independent monitoring of the medication. Given the widespread underreporting, the current one after all can in no way be a scientific argument.

A number of elements should be taken into consideration. Next, they are referred to in the form of question and answer.

Are the HPV vaccines Gardasil and Cervarix relevant to public health?

Cervical cancer is the second most common cancer in women worldwide, but in Europe this cancer amounts only to 15% of cancers in women (68 000 cases in 1995)[4]. The prognosis of cervical cancer is relatively favourable in terms of life expectancy. In Europe 62% of women with cervical cancer are still alive after 5 years[5]. The mortality is thus about a third of the incidence. In developed countries cervical cancer comes only on the 7e place, much behind breast cancer, colon, stomach and lung cancer, also behind endometrial and ovarian cancer[6].

According to the model-based studies of the firms, in optimal conditions (100% efficacy) these vaccines would prevent 70% of cervical cancers. This is up to now only a hypothesis, no 'evidence based medicine'.

For example, in the Netherlands the reality is completely different.

A cross-sectional study, part of a large prospective epidemiologic study performed among 2065 unscreened women aged 18 to 29 years gave a point prevalence of 19% HPV-types 16 (2.8%) and 18 (1.4%) were found concomitantly in only 3 women (0.1%). There was an increase in

HPV prevalence till 22 years. Multivariate analysis showed that number of lifetime sexual partners was the most powerful predictor of HPV positivity, followed by type of relationship, frequency of sexual contact, age, and number of sexual partners over the past 6 months[7].

In this Dutch population at the most around 4% of the female population might have benefitted from vaccination! As for the Danish situation: should we vaccinate 500 000 women to prevent a possible infection in 20 000 unscreened women, knowing that promiscuous behaviour and sex at a young age increase the risk and that this STI for a greater part can be avoided[8]? In these unscreened women at most a few hundred will develop cervix cancer, what could be by avoided through a cheaper screening.

In addition, in any case this screening remains needed for the 30% not covered dangerous HPV infections. Therefore in the Netherlands was advised not to take up the vaccine in the vaccination program[9].

Assessor's comments

Cervical cancer is a vaccine preventable infectious disease and one of the world's deadliest forms of cancer for women, responsible for more than 270 000 deaths annually, 85% of which occur in developing countries.

The 2013 World Health Assembly identified cervical cancer as among the priority interventions in the action plan for the prevention and control of noncommunicable diseases (NCDs) 2013-2020, which was agreed by Member States, committing them to including cervical cancer and other NCD interventions in national health plans.

The position of the WHO is summarised as follows (Human papillomavirus vaccines: WHO position paper, October 2014):

"WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and reiterates its recommendation that HPV vaccines should be included in national immunization programmes, provided that: prevention of cervical cancer and/or other HPV-related diseases constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered. Both the quadrivalent and bivalent HPV vaccines have excellent safety and efficacy profiles."

Thus, HPV vaccines are a key element in cancer prevention programmes worldwide.

In 2009 Cervarix was added to the Dutch national immunization program in the context of prevention of cervical cancer. All girls living in The Netherlands receive an invitation for vaccination in the year they turn 13.

Are the HPV vaccines Gardasil and Cervarix efficient?

Also here the pharmaceutical companies give a positive answer in terms of avoiding CIN2/3 within 5 years for the HPV-16 and 18-related, though it is not 100%.

> *By the summer of 2007, there were definitely promising results with regard to the effectiveness of the HPV vaccine in the prevention of precancerous lesions (i.e., CIN 2/3) caused by the HPV-16 and HPV-18 serotypes. However, serious questions regarding the overall effectiveness of the vaccine in the protection against cervical cancer remained to be answered, and more long-term studies were called for before large-scale vaccination programs could be recommended. Unfortunately, no longerterm results from such studies have been published since then[10].*

This statement still applies in 2015. There are no reliable follow-up studies known, independent of the firms which have been able to prove the effectiveness of the vaccine.

In addition, it was not the aim of the vaccine to prevent CIN2/3 lesions, but indeed cervix cancer. We know from the practice that on the one hand CIN2/3 lesions also can clear spontaneously what makes in fact CIN2/3 lesions an almost uncontrollable endpoint. In the long term, new lesions could also occur, eventually caused by viruses not accounted for in the used vaccines, so that they would be allowed to develop to cervical cancer.

On the other hand, in the course of their life 50 to 75 percent of all women are exposed to HPV. The virus is, however, for more than 90% of all women spontaneously cleared by the immune system within two years, and does not present any risk[11,12,13,14].

Assessor's comments

Cervarix is indicated for the prevention of premalignant genital lesions and cervical cancer, causally related to certain oncogenic Human Papillomavirus (HPV) types from the age of 9 years.

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years. Endpoints included CIN2+ associated with HPV-16 and/or HPV-18 and 12-month persistent infection.

In the Patricia trial, high efficacy against CIN 3+ was observed in the TVC-naïve cohort, irrespective of HPV type, of 93.2% (95% CI: 78.9–98.7). This cohort is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline. In the TVC analysis, the efficacy was 45.6% (95% CI: 28.8–58.7) against CIN 3+ irrespective of HPV type. In the Costa Rica trial, efficacy was 89.8% (95% CI: 39.5–99.5) against CIN 2+ associated with HPV-16/18, and 59.9% (95% CI:20.7–80.8) against CIN 2+ associated with non-HPV16/18 oncogenic HPVs.

In two further clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.

Cervarix induces some cross-protection against infection and disease caused by the phylogenetically-related non-vaccine types HPV-31, 33 and 45.

Although the exact duration of protection could not yet be established, high serum antibody titers continue to persist more than 8 years following Cervarix vaccination, with no signs of waning protection to date.

Are the vaccines safe?

According to the firms they are safe. Initially, the vaccine was compared with a placebo group being vaccinated with physiological serum, whereby the number of adverse reactions was much higher and much more serious than in the control group. After comparing 320 patients in the saline placebo group a quick move was made to an aluminium-containing placebo, in order to be able to only evaluate the effects of the active substance. However, this distorted the comparison, because no one voluntarily wants to be vaccinated with toxic aluminium, as this is not really necessary, when inoculation with a harmless saline solution can be done. The differences between Gardasil and the saline placebo group were, however, already

noticeable[15]. Here we can refer to the Vioxx scandal, where the adverse reactions in fact were known, but concealed by the firm. Here also the difference between the vaccine and the saline placebo is concealed in all publications, as the table below clearly shows. For serious adverse reactions one suddenly takes the saline and aluminium group together, perhaps to cover up the major differences between these two groups.

GARDASIL®
[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] 968

Table 6
Vaccine-related Injection-site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 5088) %	Aluminum-Containing Placebo (N = 3470) %	Saline Placebo (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritus	3.1	2.8	0.6

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 5088) %	Placebo (N = 3790) %
Systemic		
Fever	10.3	8.6
Nausea	4.2	4.1
Dizziness	2.8	2.6

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

The question about the toxicity should be taken seriously, because of the under reporting. Do doctors not inform objectively about possible side effects, because than a refusal might follow? Thereby it is well known that case reporting means a strong under reporting of reality.

> *The medical profession's ethical duty is to provide a full and accurate explanation of the benefits as well as the risks associated with a particular drug so that a patient is able to make an informed decision regarding a treatment. If a physician fails to do so and/or if financial interests take precedence over public health, breaches of informed consent guidelines may occur. For instance, presenting information in a way which promotes fear of a disease while undervaluing potential vaccine risks is likely to encourage patients to give consent to the treatment, even when the latter has no proven significant health benefit*[16].

It is also amazing that questions about the deadly accidents (India, but also in the original studies and the one's reported by the VAERS) were no longer asked, although these accidents are published. The company says that there is no link with the vaccine and that is adopted without any comment and not followed up. Probably there is no connection with the immune active substance, but this does not rule out the fact that there may be a link with the toxic additive aluminium, especially when this is compared to the administration of a saline solution.

Assessor's comments

HPV vaccines are currently considered as safe, and the WHO Advisory Committee for Vaccine Safety (GACVS) concluded in March 2014, after the review of post-licensure surveillance data from the United States, Australia, Japan and the MAH, that both HPV vaccines continue to have an excellent safety profile (*WHO 2014*).

Regarding the safety of adjuvants, some authors have hypothesised that an ASIA syndrome (autoimmunity/inflammatory syndrome induced by adjuvants) could occur following

vaccination (*Guimarães et al. 2015*). However, this hypothesis is highly controversial, and no epidemiological study has clearly evidenced this syndrome up-to-date.

At the European level, the safety profile of Cervarix is reviewed on a yearly basis via the periodic benefit-risk evaluation report. Adverse events related to potential immune-mediated disease (pIMD) following vaccination with Cervarix, as well as primary ovarian failure are currently under close safety surveillance and in depth discussed in PBRER. Moreover, as a GVP specific requirement for vaccines, vaccination failure, vaccination errors, cases with a fatal outcome, co-administration of vaccines, and vaccination anxiety-related reactions such as syncope will be also monitored. The next PBRER should be submitted by the 26/01/2016 (DLP: 17/11/2015). The safety concerns identified for Cervarix are:

Important Identified Risks	• None
Important Potential Risks	• Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination
Missing Information	• Use of HPV-16/18 vaccine in HIV-infected women or subjects with known immune deficiencies • Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine

Should the approval of the vaccines be reviewed?

> *In matters pertaining to life and death, it is essential to choose the sure thing, and, by definition, dangerous to choose otherwise. With regard to cervical cancer prevention, Papanicolaou cytological screening, done correctly, is a sure thing; HPV vaccination, done correctly, is not. We must not allow our hopes to cloud these observations. Therefore, developing countries should allocate their limited resources to cervical screening, rather than HPV vaccination, until the possibility has been excluded that HPV vaccines may be ineffective for cervical cancer prevention, or until full coverage of target demographic groups by screening services has been achieved, whichever comes first*[17].

According to this, it seems obvious to stop the general promotion of the vaccines and to develop more seriously the follow up studies. Indeed, it concerns a sexually transmitted disease that needs decades to develop and in the meantime, on the understanding that screening is provided, can be treated conveniently. It also still is not proved that one cervix cancer finally was avoided.

Assessor's comments

The scope of this referral procedure does not reflect efficacy data. The submitted safety data as well as safety data from the literature do not provide sufficient evidence to alter the benefit risk balance of Cervarix. However, the link between CRPS or POTS and vaccination with Cervarix needs to be further investigated (cfr section 6 Recommendations and Appendix A – Question 5).

What control should be implemented?

In the past various authorities have insisted upon the necessary control, so that both the efficacy of the vaccines and the adverse reactions could be mapped.

In Belgium, the Belgian Health Council (HGR)[18] has recommended to improve the screening according to the European recommendations and those of the Belgian Health care Knowledge Centre (KCE).

On the basis of a good registration of the results of the cervical screening, linked to the registration of HPV vaccinations and the cancer registration, the actual short-and long-term effects of HPV vaccination could be measured. The HGR recommends that a legal framework allowing the linking of individual HPV vaccination data to the above registers should be created and made legally possible.

A monitoring mechanism after the introduction of vaccination is needed, supported by the above mentioned registers, with attention for the long-term efficiency and adverse reactions on the vaccination, and with monitoring of circulating HPV types in various populations and specimens to detect in time any drift away to other HPV types.

Neither at European, national, nor at the regional level was this realized. This makes it impossible to identify which adverse reactions are listed, nor the effectiveness of the vaccine. After all, we ignore which women may or may not have been vaccinated. We will surely in 10-15 years not know if the fatalities from cancer were vaccinated or not, or if a possible decrease in deaths was due to the vaccine, to a better screening or to other factors such as reducing promiscuity, or a reduced use of hormonal contraception (increasing the risk of cervical cancer significantly).

Assessor's comments

At the European level, the safety profile of Cervarix is reviewed on a yearly basis via the periodic benefit-risk evaluation report. Adverse events related to potential immune-mediated disease (pIMD) following vaccination with Cervarix, as well as primary ovarian failure are currently under close safety surveillance and in depth discussed in PBRER. Moreover, as a GVP specific requirement for vaccines, vaccination failure, vaccination errors, cases with a fatal outcome, co-administration of vaccines, and vaccination anxiety-related reactions such as syncope will be also monitored. The data provided by the MAH are deeply assessed by the authorities.

Conclusion

If despite the above arguments the EMA decides to continue supporting the vaccination, the EMA could propose that the companies provide a budget for an independent control. Such action should be coordinated by the responsible government authorities in full independence from the firms.

The patients should first be objectively informed about the vaccination and the alternatives (monogamous sexual life and regular screening, what still is the general code of conduct for the vast majority of the population). Then they need to be registered in a national database, to which they themselves should be able to have access, to add any adverse reactions in consultation with the doctor. These data must be analysed by scientists who have no connection whatsoever with the pharmaceutical industry.

Assessor's comments

As already stated above, the current available data do not provide sufficient evidence to review the B/R balance of Cervarix.

Besides, it is important to highlight that, even if a PASS is performed by a MAH, the protocol must be reviewed and approved by the authorities before starting the study. Moreover, in contrast to what is published in literature, all the data obtained during the study are provided to the authorities who perform an in-depth assessment.

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Danish Health and Medicines Authority

- **Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines**

  As part of national obligations the Danish Health and Medicines Authority has prepared and shared a report regarding HPV vaccines and ADRs.

  DK Report_ADRs for HPV vaccines.pdf

  The 'Summary and conclusions' of the report is provided below.

Summary and conclusions

This report provides an overview of post-marketing safety experiences with the HPV vaccines, in terms of a description of data retrieved from the Danish, the Japanese and the WHO databases. Furthermore the most recent literature publications are quoted.

The main observations and interpretations are the following:

The introduction of the HPV vaccines in the publicly funded vaccination program did not give rise to safety concerns during the first 4 years.

From 2013 and onwards an increase in ADR reports have been noted in Denmark (exclusively in relation to use of Gardasil®, the most prominent feature being POTS) and Japan (primarily in relation to use of Cervarix®, the most prominent feature being CRPS).

The evolving safety concern has had impact on the vaccination coverage, which is declining.

Review of the 363 serious reports submitted to the Danish Pharmacovigilance Database for HPV-vaccines shows that a large proportion of the reports (34-43%) describe a symptom complex of headache, pain, fatigue, circulatory symptoms and neurological symptoms. In most cases the patients are left undiagnosed. In some cases the patients fulfill criteria for POTS. Several patients are severely physically and socially incapacitated for months / years.

The disease diagnose encompassing most of the symptoms could be a CFS-like condition. Classification is hampered though by lack of international consensus with regard to diagnostic criteria for CFS (and other syndromes).

The review highlights the necessity to evaluate (combinations of) symptoms rather than only performing separate evaluation of individual diagnoses.

Controlled trials or post-marketing epidemiology studies have not found evidence of any new or unexpected safety issues for the HPV-vaccines. However, the duration of proactive safety follow-up in the clinical trials might not have been adequate to detect the onset of symptoms. It should also be noted that post-marketing studies often rely on disease registries, and that many patients are left undiagnosed, and therefore will not appear in the registries.

Evaluation of data from WHO shows that although the number of cases for POTS is very high in Denmark, compared to the rest of the world, the symptom patterns seen in the Danish dataset is similar to reports submitted from many other countries.

A potential explanation for the huge geographic variation in the observed reporting pattern could be that similar combinations of symptoms could lead to different diagnoses depending on the country, culture or clinical setting.

Several case series have been published in recent years, and various hypotheses have been presented to explain the underlying pathophysiological mechanism, e.g. that symptoms are compatible with autonomic dysfunction, associated with vaccination due to provoked autoimmune phenomena. It is hypothesized that the dysautonomia is caused by small fiber neuropathy, but the mechanism is not clear.

The data provided in spontaneous reports cannot be used to provide evidence for causal relationship between symptoms and vaccination. It is therefore highly important to consider the possibilities for further studies to evaluate any causal relationship with the vaccination.

Assessor's comments

As discussed in question 4, it is the assessor's view that, on the basis of the available data, the link between POTS and CRPS is highly hypothetical and requests more investigation to be confirmed.

Besides, as the involvement of Cervarix vaccination and the occurrence of CRPS or POTS cannot be completely ruled out to date, it is agreed, as also suggested by the Danish and Japanese Authorities, that this potential causal relationship should be further investigated. However, it is the assessor's view that it is preferable to investigate potential associations of HPV vaccination with POTS and HPV vaccination with CRPS separately without extrapolating on hypothetical common causal patterns.