Question No. 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 and case detection methods should be clearly described and the evaluation should discuss whether the reported cases fulfil published or recognised diagnostic criteria.

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 non-serious 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.

Complex Regional Pain Syndrome (CRPS)

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 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 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 'long-term 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:

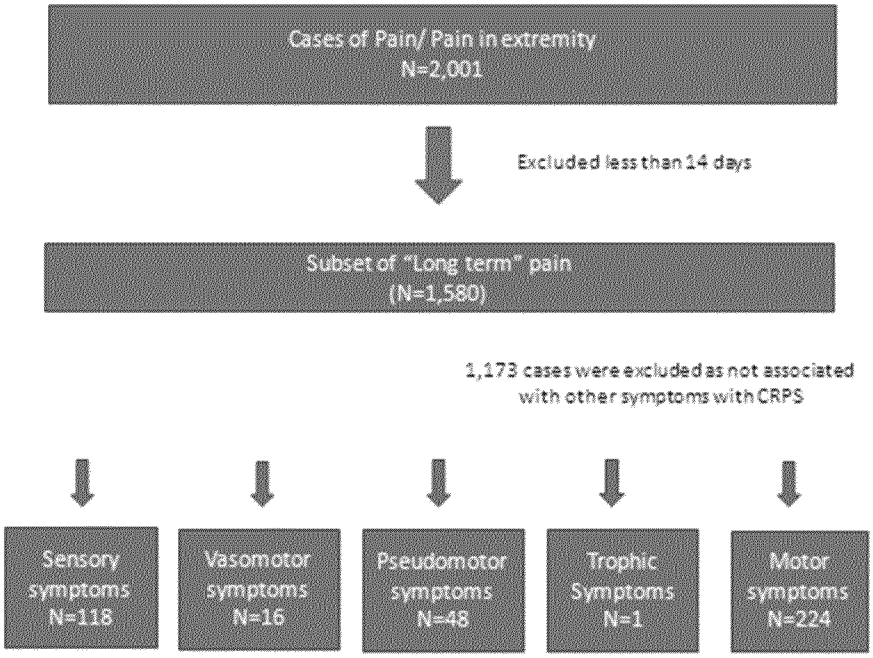
i. Subset of 'long-term pain' + sensory symptoms

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.

Postural Orthostatic Tachycardia Syndrome (POTS)

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 2010).

The company is proposing to use the case definition for POTS based on the recent publications by

Raj 2013 and Sheldon 2015, as described in the Table 5.

Table 5: Case definition of POTS

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)

The GSK'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 GSK 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 6 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.

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

Table 6: 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		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		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		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.*

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]	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.*

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 of in the GSK global safety database according to the case definition based on

Raj 2013, and Sheldon 2015, as described above.

Table 7 presents possible symptoms of POTS matched to the MedDRA PTs grouped into eight.

Table 7: 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.

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Annex 1 Overview of spontaneous and post-marketing surveillance case reports that included the MedDRA PT of CRPS (Worldwide, DLP 15 June 2015, n=49)

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	Case categories
[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.*	Confirmed case
[redacted]	12/F		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.*	Confirmed case
[redacted]	14/F		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	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	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*	Confirmed case

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	Case categories
			peripheral, Photopsia, Malaise, Urticaria, Insomnia, Dyspnoea, Hypoaesthesia, Anxiety, Confusional state, 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		hypoaesthesia, muscular weakness, oedema 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.			*the chest and leg, dyspnoea, hyperpnoea, slight fever, stomatitis, worsening of painful menses, and taste disturbance. Initially, no symptoms 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.*	Confirmed case
[redacted]	12/F		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*	Confirmed case
[redacted]	13/F		Pain, Complex regional pain syndrome, Sleep disorder, Middle insomnia, Injection site erythema, Pain in extremity, Complement factor increased, Hyperaesthesia, Arthralgia, Abdominal pain, Dyspnoea, Flank pain, Abdominal pain upper, Hyperhidrosis, Muscle twitching, Ischaemia, Somatoform disorder, Fibromyalgia	2 (02-May-11, 14-Jun-11)	2 doses administered; the onset of pain at 43 days and onset of pain in extremity at 443 days after the first dose. Duration of AEs was not reported.	Recovering/ Resolving		Unlikely case of CRPS. Paroxysmal pain in different places was reported. No other symptoms of CRPS. Somatoform disorder and fibromyalgia were noted as differential diagnoses. It was reported that subject did not require assistance in daily activities.	Unlikely case
[redacted]	13/F		Pain in extremity, Musculoskeletal pain, Injected limb mobility decreased, Muscular weakness, Feeling abnormal, Nausea, Arthralgia, Tenderness, Complex regional pain syndrome, Pain, Dizziness, Hypoaesthesia	1 (02-Aug-2012)	1 dose administered; onset of pain in extremity was reported to have experienced at 5 days after the first dose with unknown duration	Unknown		Case does not fulfil CRPS criteria based on the reported events. Brachilagia in the vaccinated arm and after numbness, no other events suggestive for CRPS. The symptoms were reported as disabling.	Unconfirmed case
[redacted]	24/F		Arthralgia, Arthropathy, Pain in extremity, Eczema, Complex regional pain syndrome	3 (02-Oct-10, 30-Oct-10, 02-	3 doses administered; the reported onset of	Recovering/Resolving		Unconfirmed case of CRPS due to insufficient evidence to meet diagnostic	Unconfirmed case

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	Case categories
				Apr-11)	pain in extremity was at 136 days after the first dose; the onset of complex regional pain syndrome was reported to be 972 days after the first dose which lasted for 33 days			criteria of CRPS. Arthralgia was reported as leading symptom in multiple location, Rheumatism was suspected but treatment discontinued due to rash. It was reported that subject did not need daily assistance in daily living due to these symptoms.	
[redacted]	17/F	[redacted]	Complex regional pain syndrome, Hypoaesthesia, Pain, Gait disturbance, Cold sweat, Malaise, Pain in extremity, Arthralgia, Myalgia, Muscular weakness, Nausea, Erythema, Palpitations, Neuropathy peripheral, Injection site pain, Hyperaesthesia, Vasodilatation, Skin discolouration, Oedema, Hyperhidrosis, Dysuria	1 (20-May-2013)	1 dose administered with hypoaesthesia, cold sweat and muscular weakness reported to have occurred soon after vaccination that lasted for 39 days; the onset of pain and pain in extremity soon after vaccination lasted between 81 and 162 days.	Recovering/Resolving		Case does not fulfil CRPS criteria. Pain was generalised, some symptoms occurred in upper limbs, other in lower limbs. Initially Guillain-Barre syndrome (Brighton Collaboration level 4) was suspected but ruled out as neurophysiological examination was without findings. It was reported that subject required assistance in daily activates due to the symptoms.	Unconfirmed case
[redacted]	12/F		Nervous system disorder, Pain, Asthenia, Back pain, Muscular weakness, Asterixis, Gait disturbance, Hypoaesthesia, Sensory disturbance, Complex regional pain syndrome, Myalgia	3 (22-Aug-11, 26-Sep-11, 07-Mar-12)	3 doses administered; the onset of pain was reported at 8 days after the first dose; other symptoms were reported to have occurred between 404 and 663 days with unknown duration.	Not Recovered/Not Resolved		Unlikely case of CRPS. Reported events included generalised pain, walking difficulties, limb numbness and sensory aberrations. First symptom after the 1st dose, but subjects completed vaccination course with 3 doses. No abnormalities were observed in a hospital. It was reported that subject did not require assistance in daily activities.	Unlikely case
[redacted]	12/F		Complex regional pain syndrome, Pain in extremity, Musculoskeletal stiffness, Haemorrhage subcutaneous	1 (20-May-2013)	1 dose administered; the onset of pain in extremity was reported to have occurred at 1 day after the first dose with unknown duration.	Unknown	Current Condition:Von Willebrand's disease	Unlikely case of CRPS. Reported symptoms included pain in the area between the left buttock and the femoral region which persisted for 2 weeks and then followed by stiffness of the left knee. It was reported that it is unknown if subject required assistance in her daily activities.	Unlikely case
[redacted]	13/F		Complex regional pain syndrome, Arthralgia, Dysstasia, Gait disturbance, Skin exfoliation, Bursitis, Pyrexia, Back pain,	1 (21-Feb-2012)	1 dose administered; the onset of complex regional pain syndrome	Recovered/Resolved		Unlikely case of CRPS. Reported symptoms included severe right medial knee pain, difficulty in standing and	Unlikely case

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	Case categories
			Psychosomatic disease, Myalgia, Hyperaesthesia		was reported to have occurred at 360 day after the first dose.			walking and myalgia. Psychosomatic disorder and bursitis were mentioned. No signs of sudomotor and throphic disturbances. It was not reported that daily activities were impacted.	
[redacted]	13/F	[redacted]	Urticaria, Complex regional pain syndrome, Malaise, Swelling face, Facial pain, Pain, Tenderness, Nausea, Arthralgia, Asthenia, Abdominal tenderness, Migraine, Headache, Hyperaesthesia, Oedema	3 (Aug-12, Oct-12, 29-Mar-13)	3 doses administered; the onset of pain started at 40 days after the first dose with unknown duration.	Recovering/Resolving	Current Condition:Epilepsy	Unlikely case of CRPS. Reported symptoms included urticarial, migrated pain, migraine, swelling of face, physical deconditioning, lower abdominal tenderness, lower jaw tenderness, tenderness of arm, tender back and arthralgia. It was reported that subject did not require assistance in daily activities.	Unlikely case
[redacted]	14/F		Complex regional pain syndrome, Illusion, Pain, Malaise	2 (07-Jan-13, 18-Feb-13)	2 doses administered; the onset of symptoms of pain was unknown; CRPS onset was reported as 117 days after the first dose.	Recovering/Resolving		Case does not fulfil CRPS criteria. Pain was reported as generalised, it was unknown whether other symptoms of CRPS occurred or not. The subject did not require assistance in daily activates due to the symptoms.	Unconfirmed case
[redacted]	14/F		Injection site pain, Injection site hypoaesthesia, Pain in extremity, Hypoaesthesia, Insomnia, Musculoskeletal stiffness, Complex regional pain syndrome, Irritability, Temperature intolerance	3 (28-Sep-11, 01-Nov-11, 28-Mar-12)	3 doses administered; onset of pain in extremity and hypoaesthesia was 105 days before the first dose that lasted for 981 days since the date of first onset.	Unknown		Case does not fulfil CRPS criteria. Complaints of pain NOS at injection site and numbness, brachialgia, numbness in both legs. It was also reported that CRPS was ruled out after consultation at university hospital. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	16/F		Headache, Arthralgia, Gastrointestinal disorder, Adjustment disorder, Complex regional pain syndrome	3 (Aug-11, Sep-11, Feb-12)	3 doses administered; the onset and/or duration of AEs were not reported.	Not Recovered/Not Resolved		Case does not fulfil CRPS criteria. Only arthralgia was reported. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	16/F		Fibromyalgia, Complex regional pain syndrome, Pain, Headache, Malaise, Pyrexia, Irritable bowel syndrome, Abdominal pain, Diarrhoea, Hyperhidrosis	3 (Mar-12, Apr-12, Oct-12)	3 doses administered; the onset of pain started at 379 days after the first dose with unknown duration. CRPS was reported at 410 days after the first dose.	Recovered/Resolved	Current Condition:Headache, Type IIa hyperlipidaemia, Arthralgia	Case does not fulfil CRPS criteria. Arthralgia and headache were reported. No symptoms of skin hypersensation, difference of skin temperature, no symptoms of skin discolouration, oedema, sweating disturbance, muscular weakness, tremor, dystonia were noted. Fibromyalgia also reported and could	Unconfirmed case

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	Case categories
								be an alternative diagnosis. It was not reported that daily activities were impacted.	
[redacted]	13/F	[redacted]	Pyrexia, Arthralgia, Complex regional pain syndrome, Pain, Muscular weakness, Soft tissue disorder	3 (29-Sep-12, 26-Oct-12, 25-Mar-13)	3 doses administered; the onset and/or duration of AEs were not reported.	Recovered/Resolved	Current Condition:Seasonal allergy	Case does not fulfil CRPS criteria based on the reported events: generalised joint pain, arthralgia, spontaneous pain and muscular weakness at unspecified location were reported. It was reported that these events were disabling.	Unconfirmed case
[redacted]	16/F		Complex regional pain syndrome, Myalgia, Musculoskeletal pain, Arthralgia, Gait disturbance, Injected limb mobility decreased, Chest pain, Tenderness, Pain, Joint contracture	1 (01-Oct-2013)	1 dose administered; onset of CRPS at 12 days and injected limb mobility at 18 days after the first dose with unknown duration.	Not Recovered/Not Resolved		Case does not fulfil CRPS criteria: presented with spontaneous pain in shoulder, knee and myalgia. Other sings of CRPS were absent. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	12/F		Headache, Muscular weakness, Gait disturbance, Injection site pain, Swelling, Injected limb mobility decreased, Hypoaesthesia, School refusal, Mental impairment, Abulia, Complex regional pain syndrome, Arthralgia, Pain, Menstruation irregular, Dizziness	3 (26-Aug-11, 26-Sep-11, 14-Feb-12)	3 doses administered; onset of muscular weakness at 97 days after the first dose. Other AEs were reported with unknown onset and/or duration.	Recovering/Resolving		Case does not fulfil CRPS criteria. The subject experienced walking difficulties, muscular weakness and headache, arthralgia. Locations of other symptoms were not reported. It was reported that subject required assistance in daily activities.	Unconfirmed case
[redacted]	14/F		Complex regional pain syndrome, Pain in extremity	1 (date not reported)	1 dose administered; onset and/or duration of AEs were not reported.	Unknown		MHLW expert case (duplicate possible): unconfirmed CRPS. No description of pain was provided, as well as other symptoms of CRPS. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	17/F		Complex regional pain syndrome	1 (date not reported)	1 dose administered; onset and/or duration of AEs were not reported.	Unknown		MHLW expert case (duplicate is possible): unconfirmed CRPS. No description of pain was provided, as well as other symptoms of CRPS. It was not reported that daily activities were impacted	Unconfirmed case
[redacted]	15/F		Complex regional pain syndrome	1 (date not reported)	1 dose administered; onset and/or duration of AEs were not reported.	Unknown		MHLW expert case (duplicate possible): unconfirmed CRPS. No description of pain was provided, as well as other symptoms of CRPS. It was not reported that daily activities were impacted.	Unconfirmed case

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	Case categories
[redacted]	32/F	[redacted]	Depressed level of consciousness, Pyrexia, Movement disorder, Gait disturbance, Complex regional pain syndrome	1 (date not reported)	1 dose administered; onset and/or duration of AEs were not reported.	Unknown		MHLW expert case (duplicate is possible): unconfirmed CRPS. No description of pain was provided, as well as other symptoms of CRPS. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	14/F		Complex regional pain syndrome, Pain, Muscular weakness, Orthostatic intolerance	2 (30-Aug-11, 30-Sep-11)	2 doses administered; onset of pain, muscular weakness and CRPS at 77 days after the first dose with unknown duration.	Recovering/Resolving		Case does not fulfil CRPS criteria. No description of pain was provided, only muscular weakness was reported as an additional symptom of CRPS. Not clear whether events concern injected limbs. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	14/F		Pain in extremity, Tremor, Abasia, Sensory disturbance, Muscular weakness, Fall, Decreased appetite, Eating disorder, Headache, Dizziness, Gait disturbance, Somatoform disorder, Complex regional pain syndrome, Mental disorder, Eye pain, Diplopia, Pain, Clumsiness, Panic reaction, Hyperacusis, Hyperaesthesia, Dyskinesia, Anxiety disorder, Limb discomfort, Peripheral coldness, Myoclonus, Motor dysfunction, Orthostatic hypotension	3 (22-Feb-11, 24-Mar-11, 12-Sep-11)	3 doses administered; onset of muscular weakness, pain in extremity and tremor at 509 days after the first dose with unknown duration.	Recovering/Resolving	Historical Condition:Attention deficit/hyperactivity disorder	Case does not fulfil CRPS criteria based on the reported events. Started with sharp pain in eyes and subject felt down with left-side muscular weakness. All other symptoms were reported in lower limbs. Pain in hand was reported as uncertain inching pain. Hyperaesthesia was reported without further details. The symptoms were reported as disabling.	Unconfirmed case
[redacted]	20/F		Injected limb mobility decreased, Skin discolouration, Peripheral swelling, Pain in extremity, Musculoskeletal pain, Headache, Nausea, Dizziness, Syncope, Hypoaesthesia, Muscular weakness, Peripheral coldness, Oedema peripheral, Chest pain, Dyspnoea, Hyperventilation, Pyrexia, Stomatitis, Dysmenorrhoea, Dysgeusia, Memory impairment, Urticaria, Injection site pain, Grip strength decreased, Photopsia, Malaise, Asthenia, Complex regional pain syndrome	3 (08-Aug-11, 06-Sep-11, 07-Feb-12)	3 doses administered; the onset and/or duration of AEs were not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Pain after 1st dose and severe pain and change in the colour that lasted for several hours after the 2nd dose. After only pain persisted and was also reported in lower limbs, chest together with oedema of lower limbs. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	13/F		Complex regional pain syndrome, Peripheral coldness, Pallor, Skin discolouration, Peripheral swelling, Pain in extremity	1 (date not reported)	1 dose administered; the date of vaccination was not reported but the duration of pain in extremity, skin discoloration and CRPS was reported to last for 9 days.	Resolved	Historical Condition:No adverse event	Unconfirmed case of CRPS due to insufficient evidence to meet diagnostic criteria of CRPS. Only some pain was reported on movement. The vaccinated arm was pale, cold and swollen; which spontaneously resolved on 3 occasions each lasting no more than 15 minutes during 1st day. The condition	Unconfirmed case

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	Case categories
								completely resolved in 7 days. It was not reported that daily activities were impacted.	
[redacted]	14/F	[redacted]	Complex regional pain syndrome, Injection site haemorrhage, Hypoaesthesia, Peripheral swelling, Skin discolouration, Peripheral coldness, Muscular weakness, Movement disorder, Idiosyncratic drug reaction	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unresolved	Historical Condition:No adverse event	Unconfirmed case of CRPS due to insufficient evidence to meet diagnostic criteria of CRPS. Reported symptoms included numbness, muscular weakness and swollen fingers. Reflexes were normal and no sensory abnormalities were noted. It was not reported that daily activities were impacted	Unconfirmed case
[redacted]	14/F		Complex regional pain syndrome, Peripheral swelling	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unresolved	Historical Condition:No adverse event	Unconfirmed case of CRPS due to insufficient evidence to meet diagnostic criteria of CRPS. Only reported symptom was hand swelling. No pain was reported. It was reported that event was disabling.	Unconfirmed case
[redacted]	?/F		Complex regional pain syndrome, Injection site pain, Injection site swelling, Injection site inflammation, Hypokinesia, Skin discolouration	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Unconfirmed case of CRPS due to insufficient evidence to meet diagnostic criteria of CRPS. Pain without further details, swelling at injection site, lack of movement, inflammation at injection site and hand changing in colour were reported. It was not reported that daily activities were impacted	Unconfirmed case
[redacted]	12/F		Contusion, Swelling, Skin lesion, Pain, Complex regional pain syndrome	1 (date not reported)	1 dose administered; the date of vaccination was not reported; the onset of pain at 40 days after vaccination that lasted for 14 days.	Unresolved		Unconfirmed case of CRPS due to insufficient evidence to meet diagnostic criteria of CRPS. Reported symptoms included contusion, swelling, skin lesion and pain located over the dorsum of the hands, feet, iliac crests or face with onset of 10 days after 2nd dose. It was not reported that daily activities were impacted.	Unconfirmed case
[redacted]	60/F		Monoplegia, Complex regional pain syndrome, Myositis, Inflammation, Pain in extremity, Injected limb mobility decreased, Sleep disorder, Weight decreased, Injection site pain	1 (date not reported)	1 dose administered; onset of pain in extremity and injected limb mobility decreased at 1 week after the first dose with unknown duration.	Unknown		Case does not fulfil CRPS criteria. Pain and paralysis were reported in the vaccinated limb, which prevent subject daily activity. Radiating injection pain was observed after 1st injection, but the subject received 2nd dose in the	Unconfirmed case

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	Case categories
								same arm. Some inflammation markers were positive (NOS) and muscle biopsy shows fibrosis.	
[redacted]	13/F	[redacted]	Complex regional pain syndrome	1 (19-Jul-2011)	1 dose administered; onset of CRPS on day on first vaccination. No other signs and symptoms were reported.	Recovering/Resolving	Current Condition:Wheelchair user	Case does not fulfil CRPS criteria based on the reported events. Literature case. No details on pain and other symptoms/signs were reported only that 3 limbs were affected by CRPS. It was not reported that event was disabling.	Unconfirmed case
[redacted]	16/F		Complex regional pain syndrome, Orthostatic intolerance, Orthostatic hypotension, Arthralgia, Pain in extremity, Asthenia, Body temperature increased, Fatigue, Tremor, Pain, Erythema, Tenderness, Gait disturbance, Pallor, Syncope, Fasciitis	1 (0ct-2011)	2 doses administered; the onset of tremor, pain and pain in extremity at 258, 472 and 806 days after the first dose; duration of these AEs were not reported.	Unknown	Historical Condition:Asthma, Dermatitis atopic	Unlikely to be CRPS. Literature case. Experienced knee arthralgia, which spread over the body, then pain appeared in calves and tremor. Neurological examination did not find abnormalities in muscle power and sensation. It was reported that symptoms were disabling.	Unlikely case
[redacted]	13/F		Complex regional pain syndrome, Orthostatic intolerance, Hyperventilation, Headache, Pain in extremity, Monoparesis, Tremor, Gait disturbance, Hyperpathia	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. Limb pain NOS, numbness, tremor, gait disturbance and paresis and decreased temperature in toe were reported. All in unspecified limb. It was reported that symptoms were disabling.	Unconfirmed case
[redacted]	15/F		Complex regional pain syndrome, Pyrexia, Monoparesis, Tremor	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. Pain NOS, tremor, paresis and decreased temperature in toe were reported, all in unspecified limb. It was reported that symptoms were disabling.	Unconfirmed case
[redacted]	15/F		Complex regional pain syndrome, Orthostatic intolerance, Orthostatic hypotension, Headache, Pain in extremity, Tremor, Peripheral coldness, Hyperhidrosis	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. Headache, limb pain NOS, limb tremors, decreased skin temperature in toe and over sweating were reported, it is unknown if all symptoms were reported in the same limb or not. It was reported that	Unconfirmed case

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	Case categories
								symptoms were disabling.	
[redacted]	15/F	[redacted]	Complex regional pain syndrome, Orthostatic intolerance, Postural orthostatic tachycardia syndrome, Pain in extremity, Tremor, Peripheral coldness	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. No description of pain was provided, only limb pain NOS, limb tremor NOS and decreased temperature in toe. It was reported that symptoms were disabling.	Unconfirmed case
	16/F		Complex regional pain syndrome, Pain in extremity, Gait disturbance	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events: limb pain NOS and gait disturbance were only reported. It was not reported that event was disabling.	Unconfirmed case
	16/F		Complex regional pain syndrome, Pain in extremity, Headache, Monoparesis, Gait disturbance, Hyperpathia	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. Limb pain NOS, limb paresis, gait disturbance and hyperpathy were reported. It was reported that these events were disabling.	Unconfirmed case
	16/F		Complex regional pain syndrome, Arthralgia, Pain in extremity, Monoparesis, Gait disturbance, Hyperpathia	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. Arthralgia, limb pain NOS, limb paresis, gait disturbance and hyperpathia were reported. It was reported that symptoms were disabling.	Unconfirmed case
	18/F		Complex regional pain syndrome, Orthostatic intolerance, Pyrexia, Gait disturbance, Headache, Monoparesis, Hyperpathia	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. Fever, gait disturbance, headache, limb paresis and hyperpathia were reported. It was reported that symptoms were disabling.	Unconfirmed case
	17/F		Complex regional pain syndrome, Orthostatic intolerance, Muscular weakness, Headache, Pain in extremity, Monoparesis, Tremor, Peripheral coldness, Hyperpathia	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Literature case. Headache, limb pain, limb paresis, gait disturbance and hyperpathia were reported. It was reported that these events were disabling.	Unconfirmed case
	18/F		Complex regional pain syndrome, Orthostatic intolerance, Orthostatic hypotension, Somnolence, Headache, Pain in	1 (date not reported)	1 dose administered; the date of vaccination,	Unknown		Case does not fulfil CRPS criteria based on the reported events.	Unconfirmed case

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	Case categories
			extremity, Tremor, Hyperpathia, Hyperhidrosis		onset and/or duration of AEs was not reported.			Literature case. Difficulty in getting up, headache, limb pain NOS, limb tremors, hyperpathy and over sweating were reported.	
[redacted]	19/F	[redacted]	Complex regional pain syndrome, Orthostatic intolerance, Abdominal pain, Headache, Pain in extremity, Monoparesis, Gait disturbance, Peripheral coldness, Hyperpathia, Hyperhidrosis	1 (date not reported)	1 dose administered; the date of vaccination, onset and/or duration of AEs was not reported.	Unknown		Case does not fulfil CRPS criteria based on the reported events. Abdominal pain, headache, limb pain NOS, limb paresis, gait disturbance, decrease temperature in toe, hyperpathy and over sweating. It was reported that symptoms were disabling.	Unconfirmed case
[redacted]	17/F		Complex regional pain syndrome, Pain, Pyrexia, Headache, Photophobia, Hyperacusis, Parosmia, Diarrhoea, Constipation, Malaise, Arthralgia, Food allergy, Memory impairment, Menstrual disorder, Presyncope, Encephalitis, Encephalopathy, Illusion, Asthma	3 (06-Oct-11, 08-Nov-11, 30-Mar-12)	3 doses administered; onset of pain at 9 days and onset of CRPS at 222 days after the first dose. CRPS lasted for 610 days.	Not Recovered/Not Resolved		Case does not fulfil CRPS criteria based on the reported events. Only general aching without further details was reported. Concurrent encephalitis that fulfils level 4 of the Brighton collaboration criteria. It was not reported that event was disabling.	Unconfirmed case
[redacted]	Unknown		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	Unknown	Unknown	Unknown	Unknown	No information was yet encoded, the case was identified in literature, request to author has been sent.	Unclassified case
[redacted]	16/F		Complex regional pain syndrome, Muscular weakness, Pain in extremity, Monoparesis, Tremor, Gait disturbance	16/F	Unknown	Unknown	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

Annex 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, Contusion	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		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		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
G[redacted]2	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
G[redacted]0	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		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]			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]			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.*	Unclassifiable

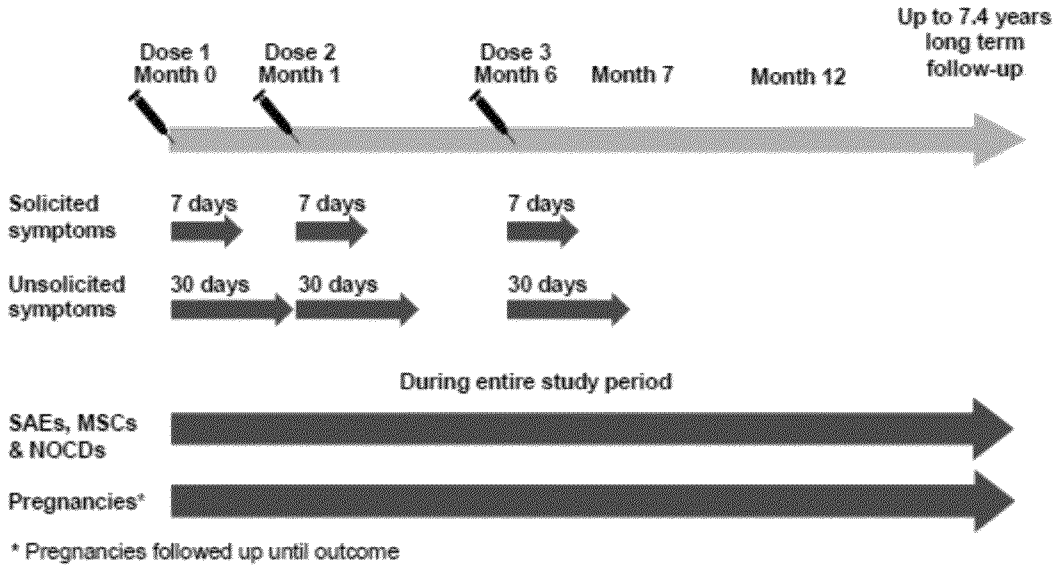
Question No. 2

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.

Response:

The outcome of analysis from clinical trial data on CRPS and POTS is presented here using the same approaches as discussed in response to Question 1.

As background information, safety assessment in GSK's HPV vaccine clinical development program is comprehensive with thorough collection of relevant safety data over extensive reporting periods after vaccine administration. 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 the subjects or the subjects' parents/guardians (in some large studies to a subset of subjects) to record solicited local and general signs and symptoms for 7 days after each vaccination.

All studies evaluate the occurrence of adverse events (AEs) following 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, as showed in Table 1.

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.

Table 1 Summary of exposure (Total vaccinated cohort)

		HPV N = 21444		CONTROL N = 20603		Total N = 42047	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Study id	HPV-001 (580299_001)	560	2.6	553	2.7	1113	2.6
	HPV-008 (580299_008)	9319	43.5	9325	45.3	18644	44.3
	HPV-009 (580299_009)	3727	17.4	3739	18.1	7466	17.8
	HPV-013 (580299_013)	1035	4.8	1032	5.0	2067	4.9
	HPV-015 (104820)	2881	13.4	2871	13.9	5752	13.7
	HPV-020PRI (107863)	91	0.4	59	0.3	150	0.4
	HPV-021 (106069)	450	2.1	226	1.1	676	1.6
	HPV-026PRI (111567)	76	0.4	76	0.4	152	0.4
	HPV-029PRI (110886)	542	2.5	271	1.3	813	1.9
	HPV-030 (111507)	494	2.3	247	1.2	741	1.8
	HPV-031 (104479)	176	0.8	178	0.9	354	0.8
	HPV-032 (104798)	519	2.4	521	2.5	1040	2.5
	HPV-033 (104951)	160	0.7	161	0.8	321	0.8
	HPV-035 (106001)	150	0.7	150	0.7	300	0.7
	HPV-036 (105926)	135	0.6	136	0.7	271	0.6
	HPV-038 (107291)	149	0.7	76	0.4	225	0.5
	HPV-058 (112022)	374	1.7	376	1.8	750	1.8
	HPV-069PRI (114590)	606	2.8	606	2.9	1212	2.9

HPV = HPV
CONTROL = CONTROL
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100

Complex Regional Pain Syndrome (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:

First, the reporting frequencies of Pain or Pain in extremity with duration of longer than 14 days from onset were similar between the groups that received HPV and control/comparator vaccines resulting in Relative Risks (RR) ≤ 1.46 with 95% Confidence intervals including 1 in each of the analyses performed as presented in Table 3, Table 4 and Table 5.

Table 3 Difference between groups in percentage of subjects reporting the occurrence of unsolicited symptoms within the 30 days (Day 0 to Day 29) post-vaccination period (Total vaccinated cohort)

	HPV N = 21444					CONTROL N = 20603					Relative Risk (HPV over CONTROL)		
				95% CI					95% CI			95% CI*	
	n*	n	%	LL	UL	n*	n	%	LL	UL	RR	LL	UL
Pain or Pain in extremity with duration of symptoms longer than 2 weeks since onset	18	18	0.08	0.05	0.13	12	12	0.06	0.03	0.10	1.44	0.65	3.28

Table 4 Difference between groups in percentage of subjects reporting the occurrence of unsolicited symptoms within the 6 months post-vaccination period (Total vaccinated cohort)

	HPV N = 21444					CONTROL N = 20603					Relative Risk (HPV over CONTROL)		
				95% CI					95% CI			95% CI*	
	n*	n	%	LL	UL	n*	n	%	LL	UL	RR	LL	UL
Pain or Pain in extremity with duration of symptoms longer than 2 weeks since onset	26	26	0.12	0.08	0.18	17	17	0.08	0.05	0.13	1.46	0.76	2.88

Table 5 Difference between groups in percentage of subjects reporting the occurrence of unsolicited symptoms during the study period (Total vaccinated cohort)

	HPV N = 21444					CONTROL N = 20603					Relative Risk (HPV over CONTROL)		
				95% CI					95% CI			95% CI*	
	n*	n	%	LL	UL	n*	n	%	LL	UL	RR	LL	UL
Pain or Pain in extremity with duration of symptoms longer than 2 weeks since onset	37	36	0.17	0.12	0.23	29	29	0.14	0.09	0.20	1.20	0.72	2.04

HPV = HPV
CONTROL = CONTROL
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

As a result of the second step of this search, the analysis did not identify any subject who reported a combination of pain/pain in extremity of duration of more than two weeks with any other possible symptoms of CRPS.

Overall, no potential cases of CRPS have been identified in this analysis. The company evaluated whether there were any differences between HPV vaccine and control groups in the occurrence of "Pain or Pain in extremity with duration of symptoms longer than 2 weeks since onset", since this is one of the leading symptoms of CRPS. 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 ≤ 1.46 and 95% Confidence intervals including 1 in each of the analyses performed.

Postural Orthostatic Tachycardia Syndrome (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.

3. ***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.

4. ***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, resulting in RRs below 1.8 with 95% Confidence intervals including 1 in each of the analyses performed as presented in Table 7, Table 8 and Table 9

Table 7 Difference between groups in percentage of subjects reporting the occurrence of unsolicited symptoms within the 30 days (Day 0 to Day 29) post-vaccination period (Total vaccinated cohort)

	HPV N = 21444					CONTROL N = 20603					Relative Risk (HPV over CONTROL)		
				95% CI					95% CI			95% CI*	
	n*	n	%	LL	UL	n*	n	%	LL	UL	RR	LL	UL
Group A	19	18	0.08	0.05	0.13	21	21	0.10	0.06	0.16	0.81	0.41	1.60
Group B	425	381	1.78	1.60	1.96	351	323	1.57	1.40	1.75	1.14	0.98	1.33
Group C	27	26	0.12	0.08	0.18	22	20	0.10	0.06	0.15	1.12	0.60	2.14
Group E	38	38	0.18	0.13	0.24	51	45	0.22	0.16	0.29	0.81	0.51	1.27
Group F	7	7	0.03	0.01	0.07	5	5	0.02	0.01	0.06	1.40	0.38	5.59
Group G	1	1	0.00	0.00	0.03	2	2	0.01	0.00	0.04	0.39	0.01	7.80
Group H	144	134	0.62	0.52	0.74	133	126	0.61	0.51	0.73	1.00	0.78	1.28

Table 8 **Difference between groups in percentage of subjects reporting the occurrence of unsolicited symptoms within the 6 months post-vaccination period (Total vaccinated cohort)**

	HPV N = 21444					CONTROL N = 20603					Relative Risk (HPV over CONTROL)		
				95% CI					95% CI			95% CI*	
	n*	n	%	LL	UL	n*	n	%	LL	UL	RR	LL	UL
Group A	27	26	0.12	0.08	0.18	25	24	0.12	0.07	0.17	1.03	0.57	1.87
Group B	474	424	1.98	1.80	2.17	394	360	1.75	1.57	1.94	1.14	0.99	1.32
Group C	34	32	0.15	0.10	0.21	28	26	0.13	0.08	0.18	1.08	0.62	1.90
Group E	49	48	0.22	0.17	0.30	58	51	0.25	0.18	0.33	0.91	0.60	1.37
Group F	10	9	0.04	0.02	0.08	5	5	0.02	0.01	0.06	1.80	0.54	6.83
Group G	1	1	0.00	0.00	0.03	3	3	0.01	0.00	0.04	0.27	0.01	3.52
Group H	187	174	0.81	0.70	0.94	165	156	0.76	0.64	0.89	1.02	0.81	1.27

Table 9 **Difference between groups in percentage of subjects reporting the occurrence of unsolicited symptoms during the study period (Total vaccinated cohort)**

	HPV N = 21444					CONTROL N = 20603					Relative Risk (HPV over CONTROL)		
				95% CI					95% CI			95% CI*	
	n*	n	%	LL	UL	n*	n	%	LL	UL	RR	LL	UL
Group A	41	40	0.19	0.13	0.25	38	37	0.18	0.13	0.25	1.04	0.65	1.68
Group B	515	461	2.15	1.96	2.35	437	397	1.93	1.74	2.12	1.13	0.98	1.29
Group C	48	44	0.21	0.15	0.28	44	40	0.19	0.14	0.26	1.01	0.64	1.59
Group E	60	58	0.27	0.21	0.35	71	64	0.31	0.24	0.40	0.88	0.60	1.27
Group F	10	9	0.04	0.02	0.08	5	5	0.02	0.01	0.06	1.80	0.54	6.83
Group G	1	1	0.00	0.00	0.03	4	4	0.02	0.01	0.05	0.21	0.00	2.20
Group H	223	208	0.97	0.84	1.11	211	201	0.98	0.85	1.12	0.96	0.79	1.17

HPV = HPV
CONTROL = CONTROL
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

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.

References:

Angelo et al, 2014 Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiology and drug safety (2014) DOI: 10.1002/pds.3554

Harden RN. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 150(2), 268-274 (2010).

Question No 3.

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

Response:

The company's position on possible risk minimisation tools is provided in response to Question 5.

The analysis of the observed number of post-marketing cases of CRPS and POTS following vaccination with Cervarix in comparison to the expected rate in the target population is provided in Annex 1.

Annex 2 provides the comprehensive review of published literature that was conducted by GSK and SP/MSD to derive the background incidence rates for CRPS and POTS for consideration in observed/expected analyses.

Annex 1: Observed-to-expected analyses of Complex Regional Pain Syndrome (CRPS) and Postural orthostatic tachycardia syndrome (POTS) with Cervarix

Complex Regional Pain Syndrome (CRPS)

Methodology

Cases

At the data lock point (15 June 2015) used for this analysis, the GSK global safety database contained 49 spontaneous case reports for Cervarix that included the MedDRA PT of CRPS for 57 094 396 (reporting rate 0.086 per 100,000 doses) doses distributed worldwide. Among these CRPS cases, [redacted] were reported in Japan for [redacted] doses distributed (reporting rate 0.57 per 100,000 doses); [redacted] cases were reported in the United Kingdom (UK) for [redacted] doses distributed (reporting rate 0.092 per 100,000 doses), and [redacted] case was reported in Republic of Korea for [redacted] doses distributed (reporting rate 0.043 per 100,000 doses).

As discussed in response to Question 1, all cases were reviewed according to the case definition proposed by Harden et al, 2010 and defined as confirmed cases of CRPS, unconfirmed cases of CRPS (due to lack of information) and unlikely cases of CRPS. Individual line listing of this cases are provided in Annex 1 of the response provided to Question 1 including case classifications as confirmed, unconfirmed and unlikely cases of CRPS..

A best-case safety scenario for Cervarix vaccine included only confirmed cases of CRPS, a mid-case 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.

Regions/ Countries

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.

Background incidence rate

de Mos et al provided an estimated background incidence rate of CRPS of 40.4 per 100,000 person-years for females in the Netherlands. The authors also provided incidences by age groups (See table 1). In the current analysis, 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. Indeed, the exposure to Cervarix and the incidence of CRPS vary by age. Consequently, the incidence and the age distribution in the Cervarix vaccinated population need to be taken into account, such that the most representative expected incidence rate is used in the analysis. However, despite some estimates for the 10-19 age stratum being publicly available, from the coverage data collected during the UK Cervarix vaccination campaign, the actual age distribution of the exposed population is not available. Therefore, as a substitute, we used the age distribution across all worldwide, Japanese, British and Korean spontaneous cases identified in the global safety database for Cervarix up to the data lock point of 1 July 2015 (refer to Table 1). The age-adjusted background incidence rates corresponding to females having been vaccinated with Cervarix was estimated by taking the weighted average of the incidence rates within each age stratum. Rationale for using the background incidence rate of de Mos et al. is provided in Annex 2.

Table 1 Background Incidence Rates (IR) by age stratum (de Mos 2007), Age-adjusted Background Incidence Rates and distribution of age at vaccination in the worldwide, Japanese, British and Korean Cervarix population

Age stratum (years)	Background IR per 100,000 person-years (de Mos et al 2006)	Age distribution (%) in spontaneous cases, Cervarix, worldwide	Age distribution (%) in spontaneous cases, Cervarix, Japan	Age distribution (%) in spontaneous cases, Cervarix, UK	Age distribution (%) in spontaneous cases, Cervarix, Republic of Korea
0-9	2	0.4	0	0.2	0.4
10-19	14.9	85.7	97	97.3	20
20-29	28	8.4	2	1.8	37.5
30-39	27.7	3.6	0.5	0.4	25.4
40-49	27.2	1.5	0.5	0.1	10
50-59	72.1	0.4	0	0.2	6.3
60-69	121.3	0	0	0	0.4
70-79	58.1	0	0	0	0
80-110	47.5	0	0	0	0
Total	40.4	100	100	100	100
Age-adjusted background IR	16.91 (worldwide) 15.29 (Japan) 15.32 (UK) 28.26 (Korea)	-	-	-	-

Exposure

The actual number of Cervarix doses administered is not available to the Company however we considered that on average 75% of doses distributed are administered. This proportion was considered plausible as it is close to the estimated figure we obtained when comparing the coverage data collected during the Cervarix vaccination campaign in the United Kingdom (http://webarchive.nationalarchives.gov.uk) and the number of doses distributed during that period. For the UK, the number of persons vaccinated, estimated from these coverage data, was used.

For all countries and region we made the assumption that all vaccinated persons received 3 doses of the vaccine, as suggested by PRAC.

Risk periods and reported fraction

In line with the recommendations made by the rapporteur and co-rapporteur team (TC on 17 July 2015), we evaluated whether the observed number of cases is lower or higher than expected, assuming different magnitudes of reported fraction and considering a range of values for the risk period.

Different risk periods post exposure to a Cervarix dose were used (ranging from 1week to 2 years, 2 years corresponding to the longest TTO for CRPS cases reported in the GSK global safety database), as well as different percentages of cases actually spontaneously reported, labelled "Reported fraction" (in a range between 1% and 100%). The reported fraction is the proportion of CRPS cases reported among all those that occurred within the risk period. For these different combinations of risk periods and reported fractions, an observed-to-expected analysis was performed in order to determine if the observed number of CRPS cases was:

* Significantly higher than expected (at a 95% confidence level)

* Higher than expected

* Lower than expected

* Significantly lower than expected (at a 95% confidence level)

These different conclusions (ccl) are illustrated in the figures below.

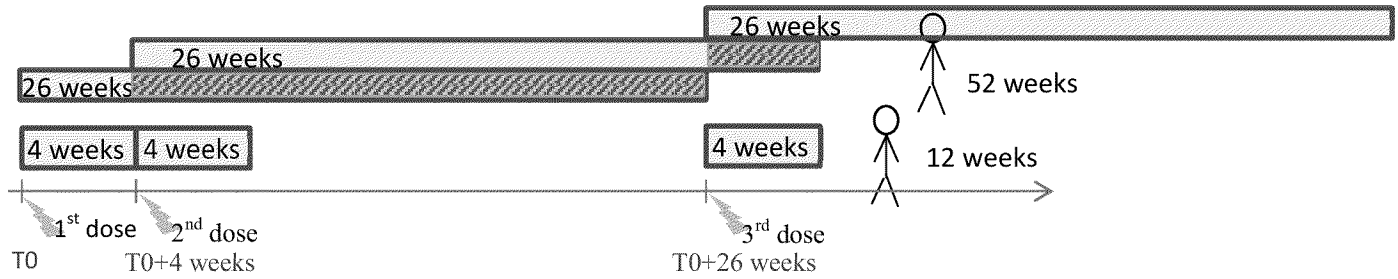
As uncertainty analysis, the O/E analysis was performed for three different safety scenarios already described above.

For each value of risk period and reported fraction the following observed and expected numbers were calculated and compared with a Poisson exact confidence interval[3] around the observed number:

$$[Observed\ number] = [Observed\ number\ of\ CRPS\ cases\ within\ the\ risk\ period]$$

$$[Expected\ number] = \frac{[Age\text{-}adjusted\ Background\ Incidence\ Rate]}{100\,000} * \frac{[Number\ of\ sold\ doses * 0.75]}{3} * \frac{[Time\ at\ risk\ per\ person\ (in\ weeks)]}{52} * [Reported\ fraction]$$

In order to avoid the double counting of time at risk per person, we used the following approach:



Considering that the recommended schedule for Cervarix vaccination is at 0, 1 and 6 months and under the assumption that each vaccinated person received 3 doses, when the Risk Period (RP) after each dose is lower or equal to 4 weeks then the Time at Risk per person in weeks (TR) is considered as being the TR=RP*3; when the RP is higher than 4 weeks but lower than 22 weeks then the TR=4+RP*2 and when the RP is higher or equal to 22 weeks then the TR=4+22+RP.

Limitations

There are several limitations to observed-to-expected analyses, and several levels of uncertainty. The major factors affecting this observed-to-expected analysis are discussed below. They relate to:

1. Limited references for background incidence rates.

2. The uncertainty on the distribution of the age at which subjects are vaccinated and the number of subjects vaccinated. We tried to overcome the uncertainty on the number of subjects vaccinated by applying a correcting factor of 0.75 to the number of doses sold.

3. The reporting biases such as underreporting, unconfirmed case details, over reporting. We tried to overcome the uncertainty on the completeness of the reporting by simulating a range of reported fractions.

4. The uncertainty around the risk period. We tried to overcome this uncertainty by considering a range of risk periods from 1 week to 1 or 2 years.

Results & Discussion:

The figures below summarise the different possible conclusions when performing the observed-to-expected analyses by using the age-adjusted incidence rate of CRPS and considering different values of risk periods and reported fractions.

Worldwide

The results of the observed-to-expected analyses for worldwide are presented in Figure 1 for the best-case safety scenario, in Figure 2 for the mid-case safety scenario and in Figure 3 for the

worst-case scenario. If we consider 1 week as risk period (time at risk per person of 3 weeks), 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.

Figure 1 **Heat map of the worldwide best-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**

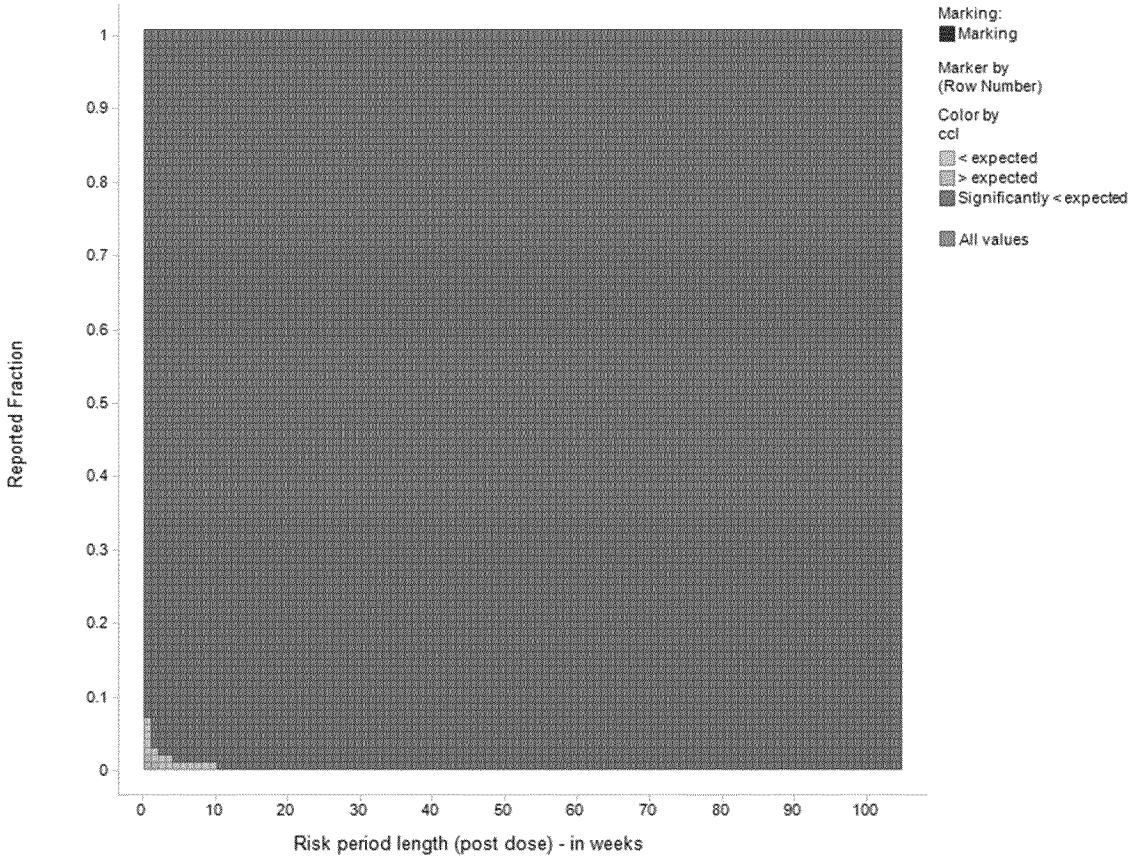


Figure 2 **Heat map of the worldwide mid-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the underreporting (two unknown parameters).**

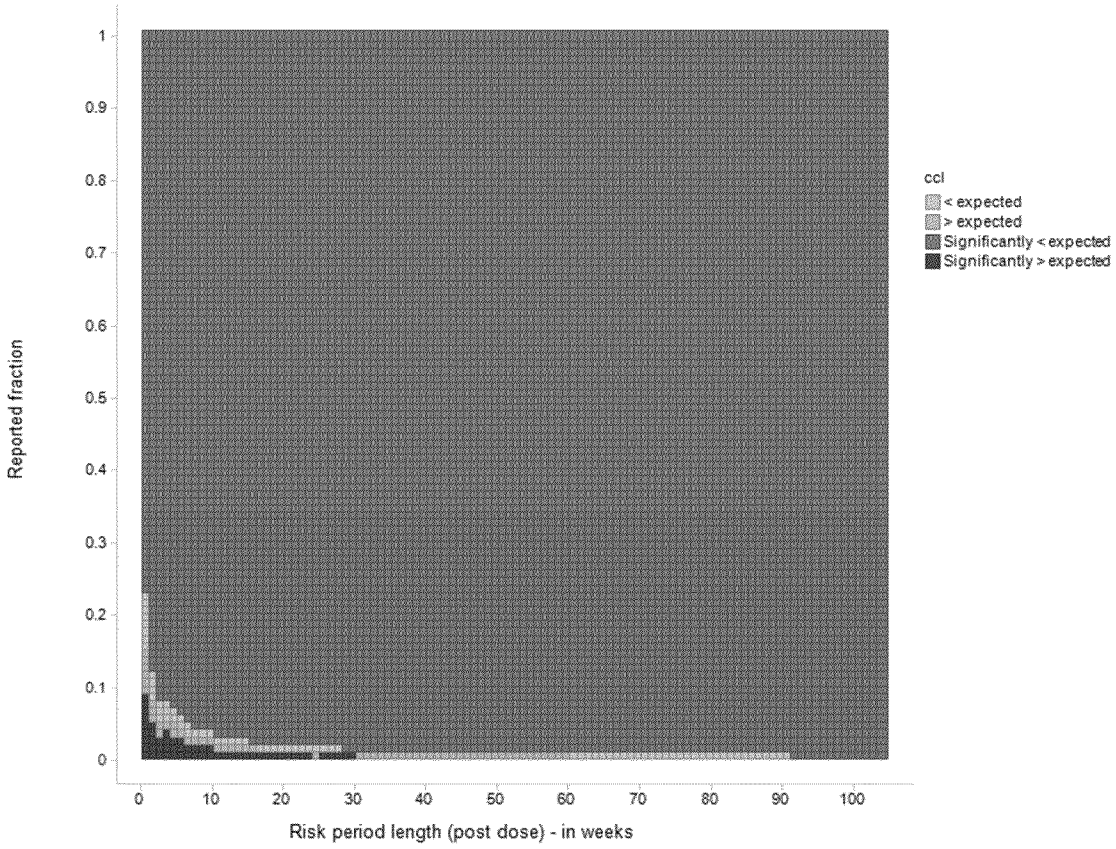
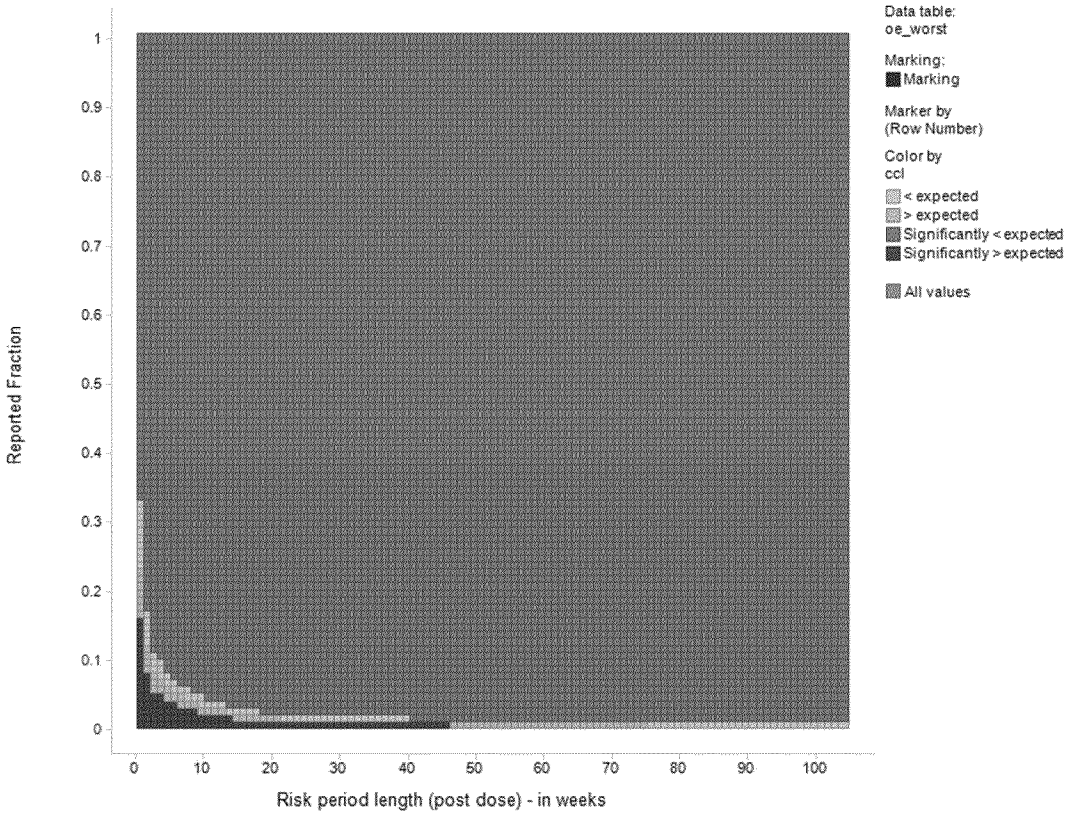


Figure 3 Heat map of the worldwide worst-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).



Japan

Similarly, Figure 4, Figure 5, Figure 6 summarise the results of the observed-to-expected analyses restricted to Japan for the best-, mid- and worst-case safety scenario, respectively. Considering a risk period after each dose of 1 week (time at risk per person of 3 weeks), 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 TTO 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.

Figure 4 **Heat map of the Japan best-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**

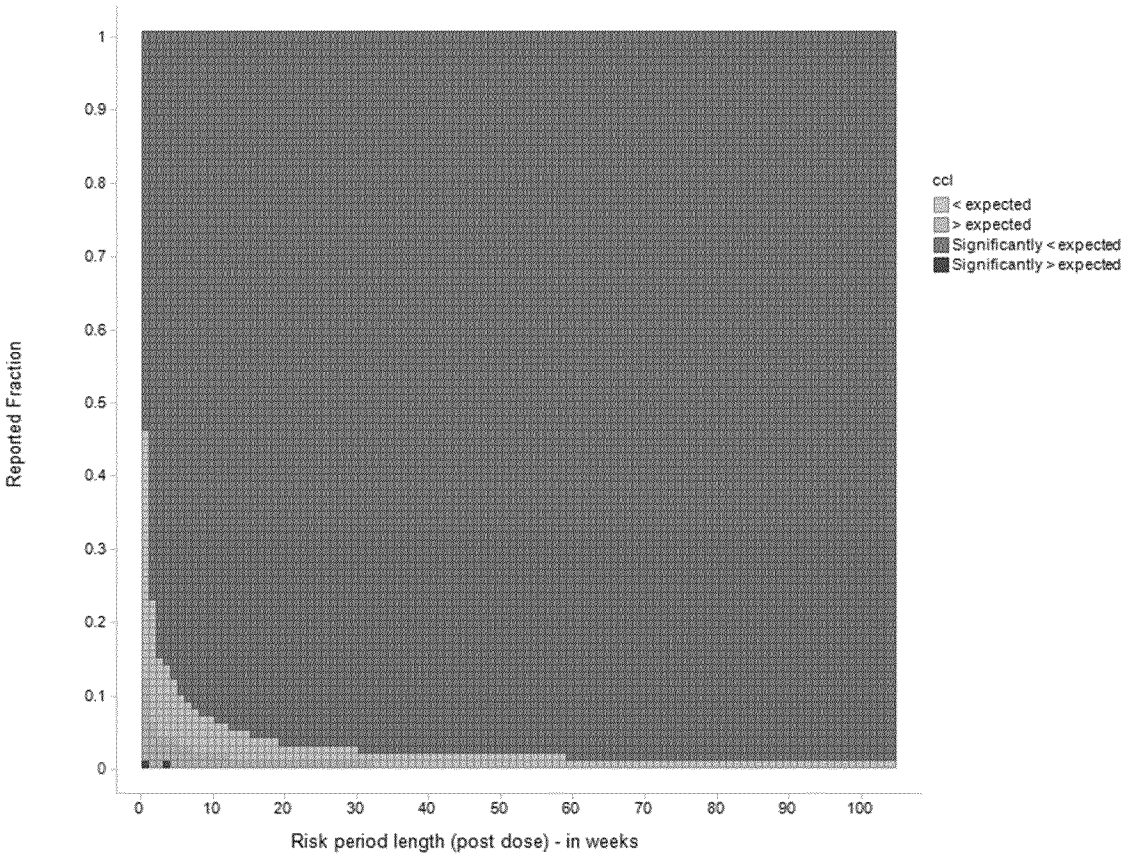


Figure 5 **Heat map of the Japan mid-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**

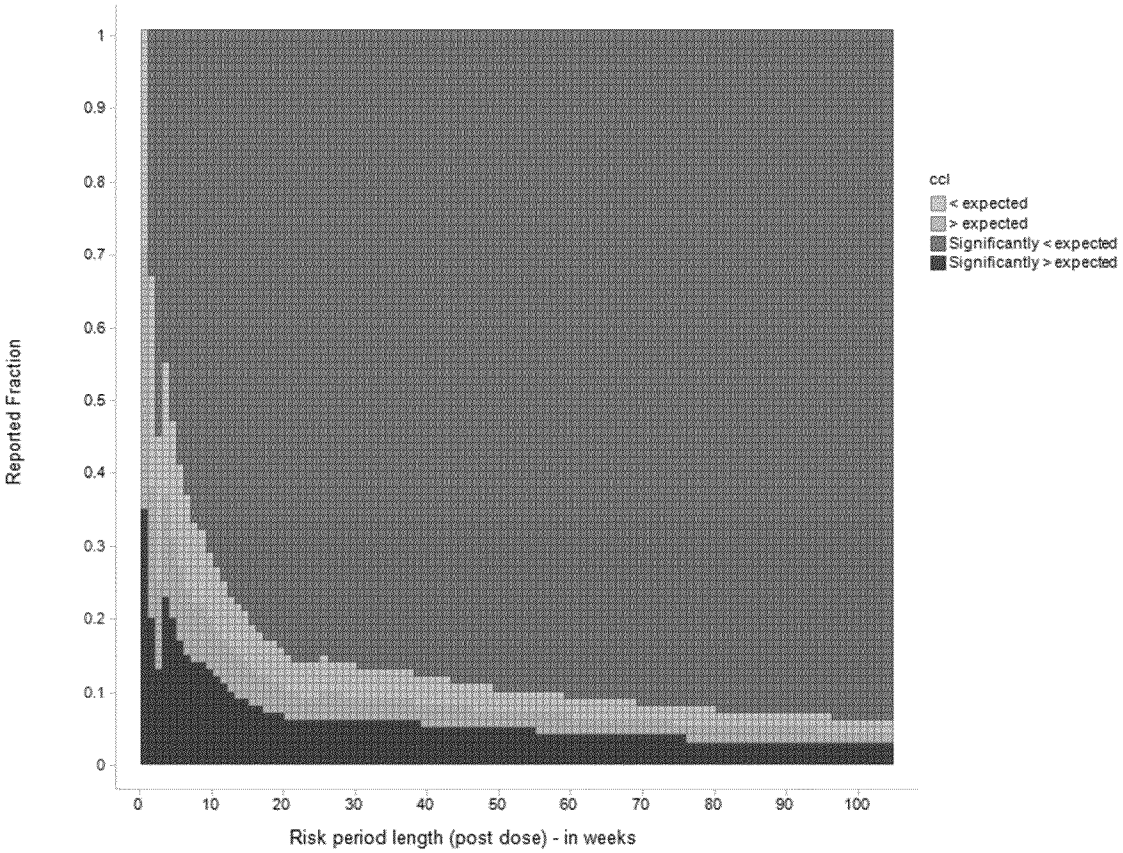
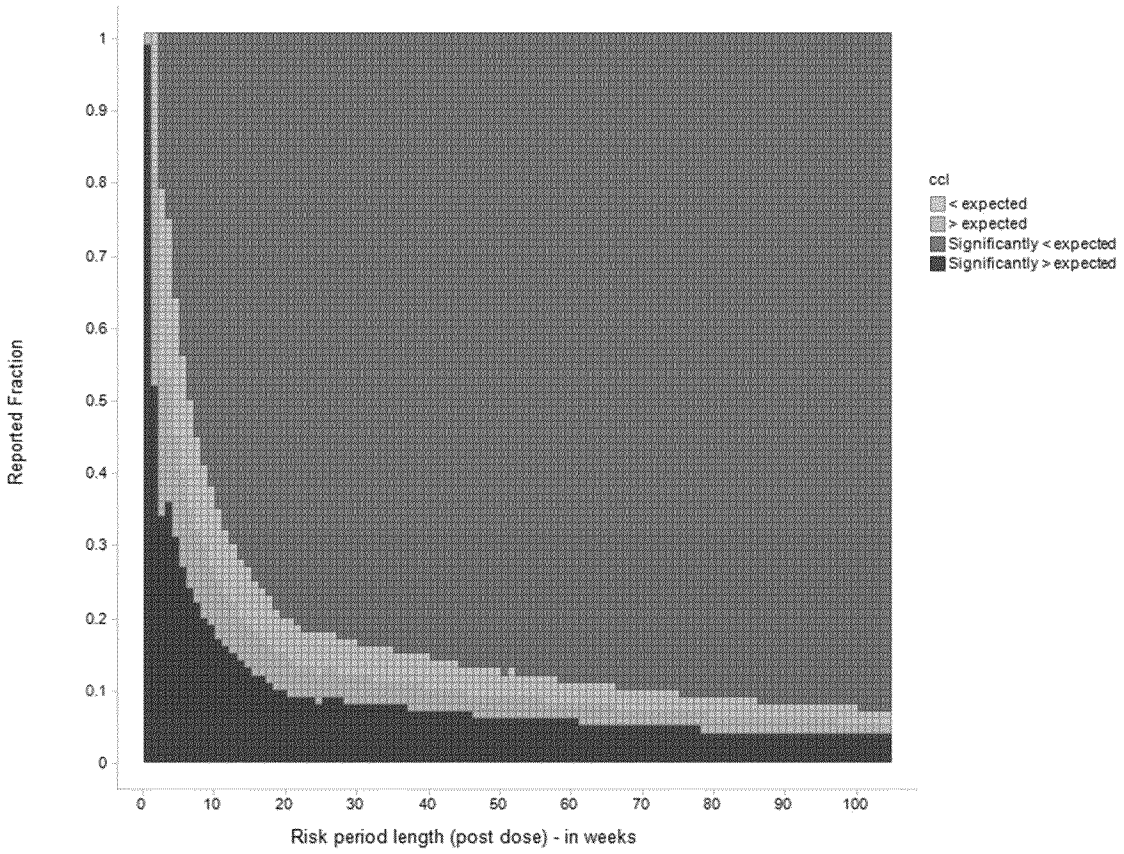


Figure 6 **Heat map of the Japan worst-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**



United Kingdom

The results of the observed-to-expected analyses for the UK are presented in Figure 7,

Figure 8 and Figure 9 for the best-, mid- and worst-case safety scenario, respectively. 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.

Figure 7 **Heat map of the UK best-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**

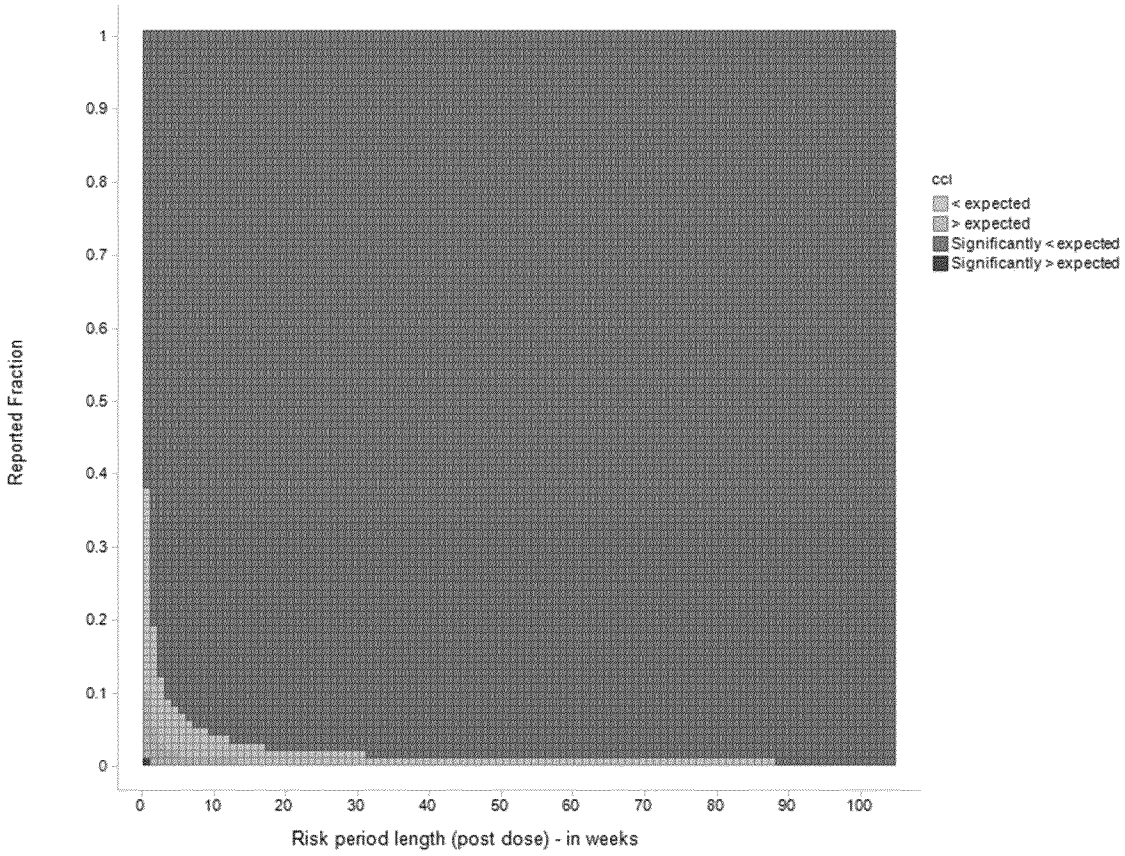


Figure 8 **Heat map of the UK mid-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**

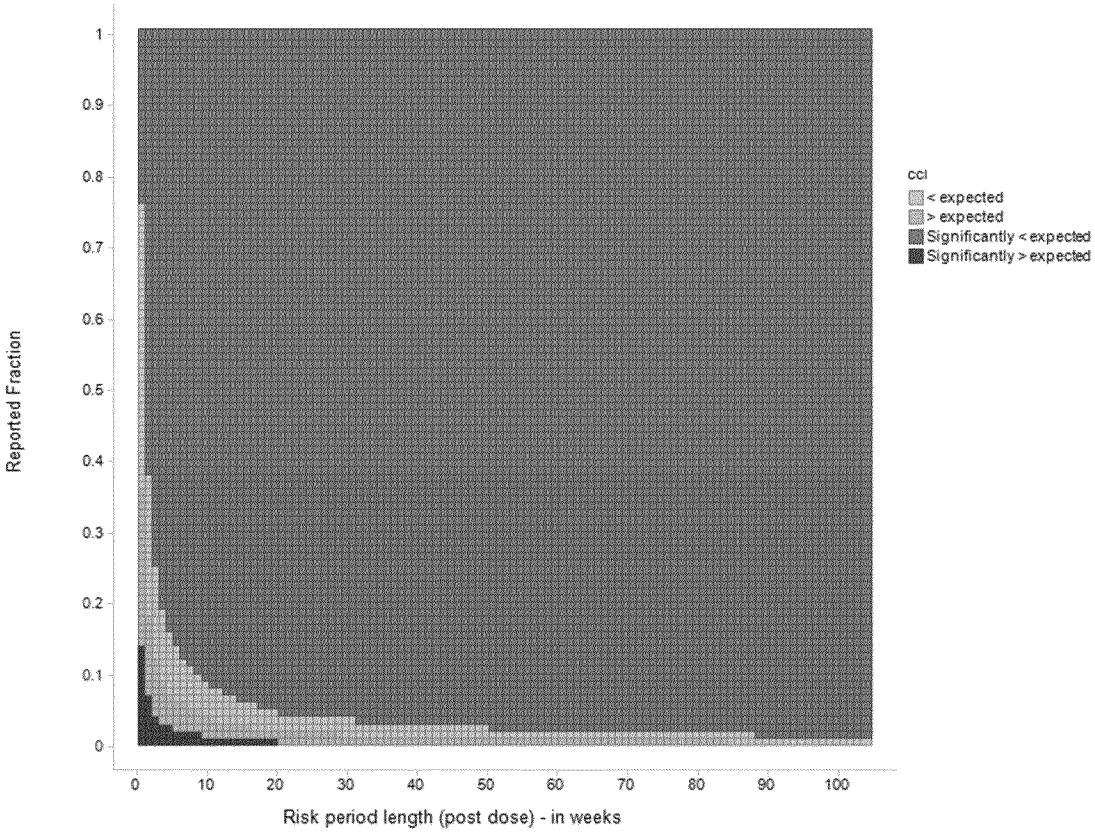
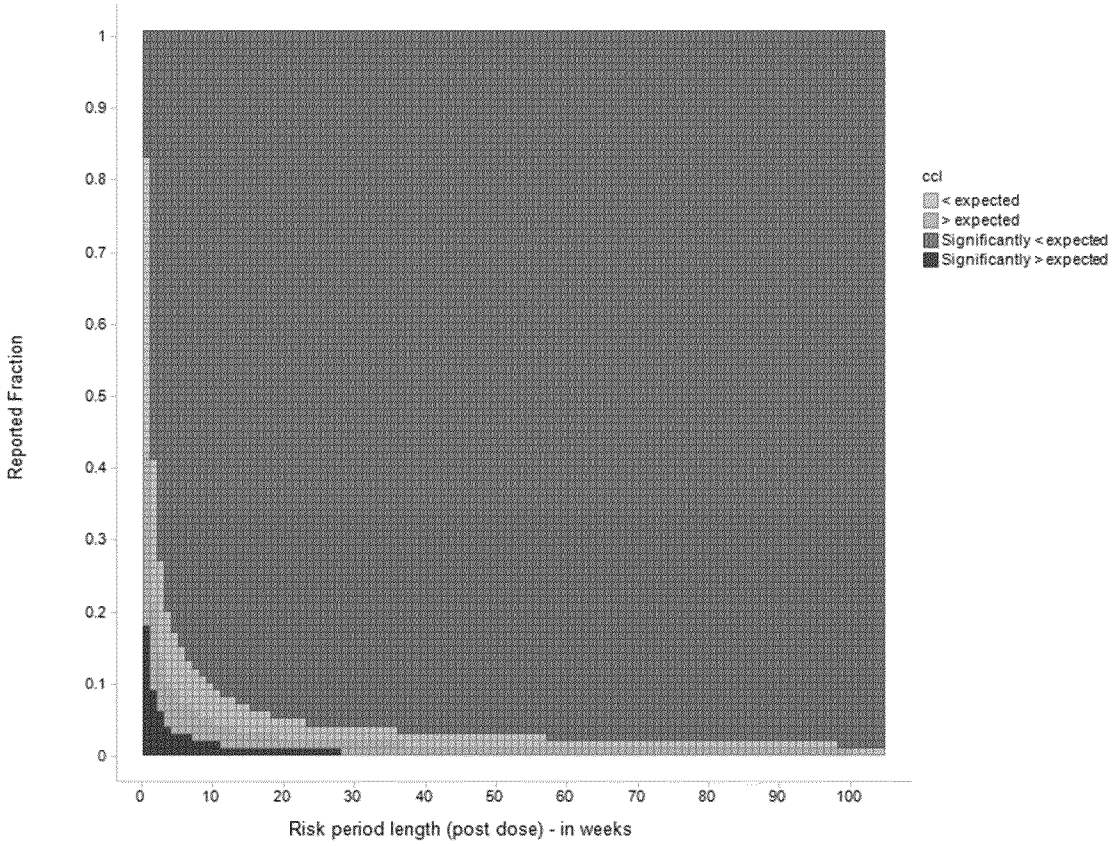


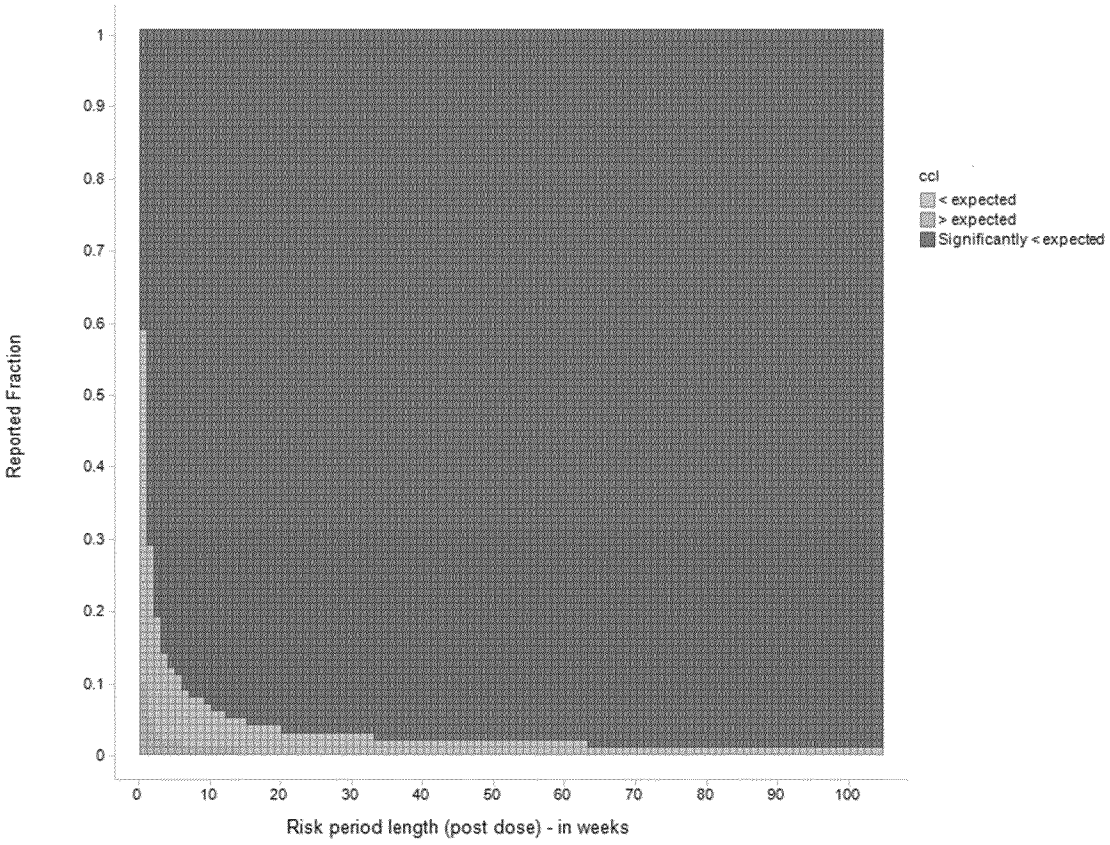
Figure 9 **Heat map of the UK worst-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**



Republic of Korea

The results of the observed-to-expected analyses for the Republic of Korea are presented in Figure 10 for the mid-case safety scenario. 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.

Figure 10 Heat map of the Korean mid-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).



Conclusion:

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.

Postural orthostatic tachycardia syndrome (POTS)

Methodology

Cases

At the data lock point (15 June 2015) used for this analysis, the GSK global safety database contained 19 spontaneous case reports for Cervarix that included the MedDRA PT of POTS for 57 094 396 (reporting rate 0.033 per 100,000 doses distributed) doses sold worldwide. 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. 1 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 (see Annex 1 in response to Question 1).

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.

Regions/ Countries

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.

Exposure

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, as suggested by PRAC.

Risk period

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).

Background incidence rates

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 table 2. Rationale for the background incidence rates used is provided in Annex 2.

Table 2 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**

Assuming different magnitudes of reported fraction and considering a range of values for the background incidence of POTS in a Cervarix vaccinated population, we assessed whether the observed number of cases was lower or higher than expected.

Different background incidence rates were simulated (in a range between 15 and 140 per 100,000 person-years) as well as different percentages of cases actually spontaneously reported, labelled "Reported fraction" (in a range between 1% and 100%). The reported fraction is the proportion of POTS cases reported among all those that occurred within the risk period. For these different combinations of simulated background incidence rates and reported fraction, an observed-to-expected analysis was performed in order to determine if the observed number of POTS cases was:

* Significantly higher than expected (at a 95% confidence level)

* Higher than expected

* Lower than expected

* Significantly lower than expected (at a 95% confidence level)

As an uncertainty analysis, the O/E analysis was performed for two different safety scenarios already described above.

For each simulated value of background incidence rate and reported fraction the following reporting rates were calculated and compared with a Poisson exact confidence interval[3] around the "observed reporting rate" (per 100,000 person-years):

$$[Observed\ Reporting\ Rate] = \frac{[Observed\ number\ of\ POTS\ cases\ within\ the\ risk\ period]}{\frac{[Number\ of\ sold\ doses * 0.75]}{100000 * 3} * \frac{[Time\ at\ risk\ per\ person\ (in\ days)]}{365.25}}$$

$$[Expected\ Reporting\ Rate] = [SimulatedBackground\ Incidence\ Rate] * [Reported\ fraction]$$

The same strategy for the risk periods was used as the one for the CRPS observed-to-expected analyses.

Limitations

There are several limitations to observed-to-expected analyses, and several levels of uncertainty. The major factors affecting this observed-to-expected analysis are discussed below. They relate to:

1. Limited references for background incidence rates. We tried to overcome this by considering a range of background incidence rates.

2. The uncertainty on the distribution of the age at which subjects are vaccinated and the number of subjects vaccinated. We tried to overcome the uncertainty on the number of subjects vaccinated by applying a correcting factor of 0.75 to the number of doses sold.

3. The reporting biases such as underreporting, unconfirmed case details, over-reporting. We tried to overcome the uncertainty on the completeness of the reporting by simulating a range of reported fractions.

4. The uncertainty around the risk period. We tried to overcome this uncertainty by considering a range of risk periods from 1 week to 1 or 2 years.

Results & Discussion

In order to limit the total number of figures presented, we used a different format than for the CRPS analysis, allowing the presentation of the different safety scenarios within the same figure.

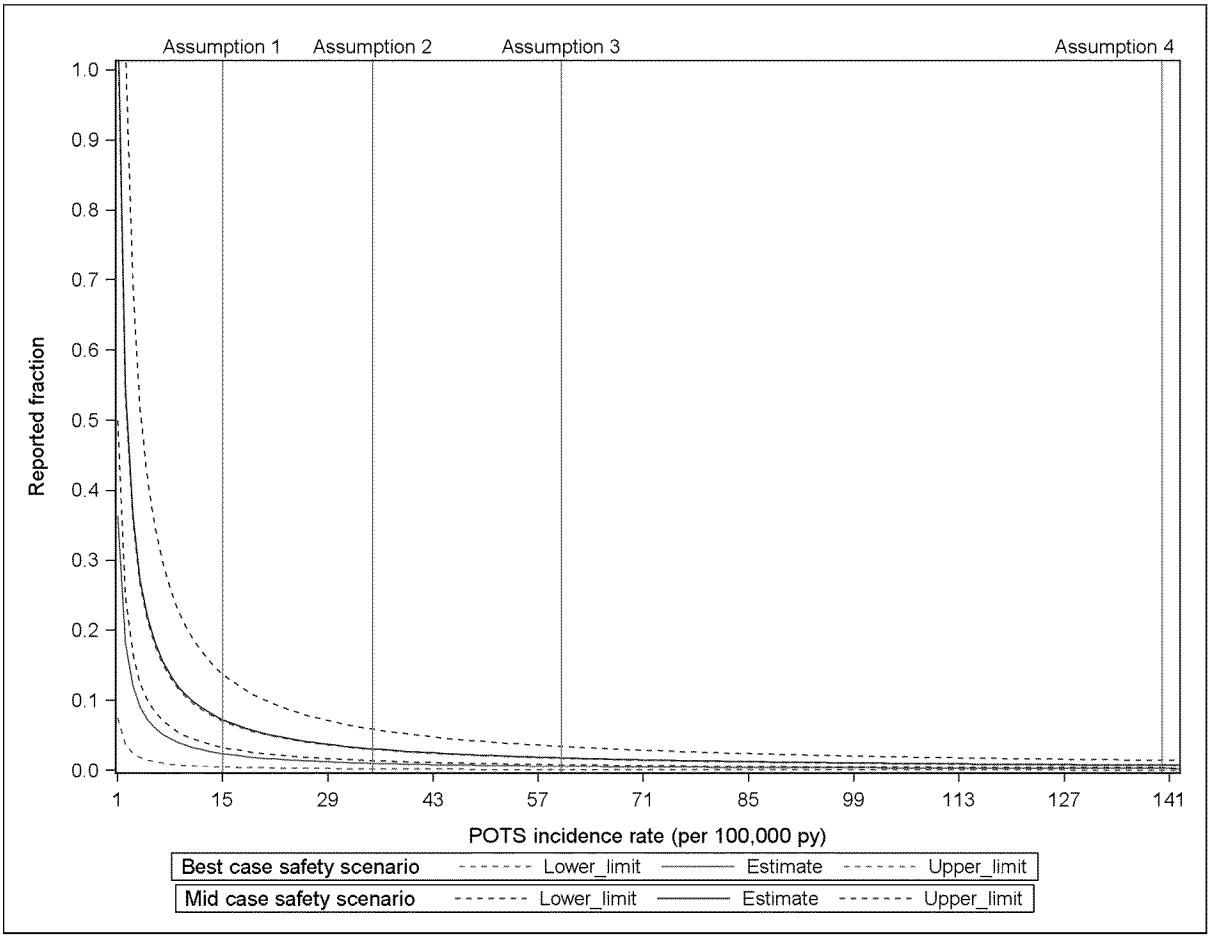
The figures below summarise the different possible conclusions when performing the observed-to-expected analyses by using a risk period of 1 week, 1 month, 6 months and 1 year and

considering different values of background incidence rates and reported fraction. The vertical lines represent the background incidence rates according to the different assumptions displayed in Table 2. In these figures, the estimate represents when the observed reporting rate equals the expected reporting rate. Above this estimate, the observed is lower than expected rate, and above the upper limit the observed is significantly lower than expected. Following the same logic: below the estimate the observed is higher than expected, and below the lower limit the observed is significantly higher than expected.

Worldwide

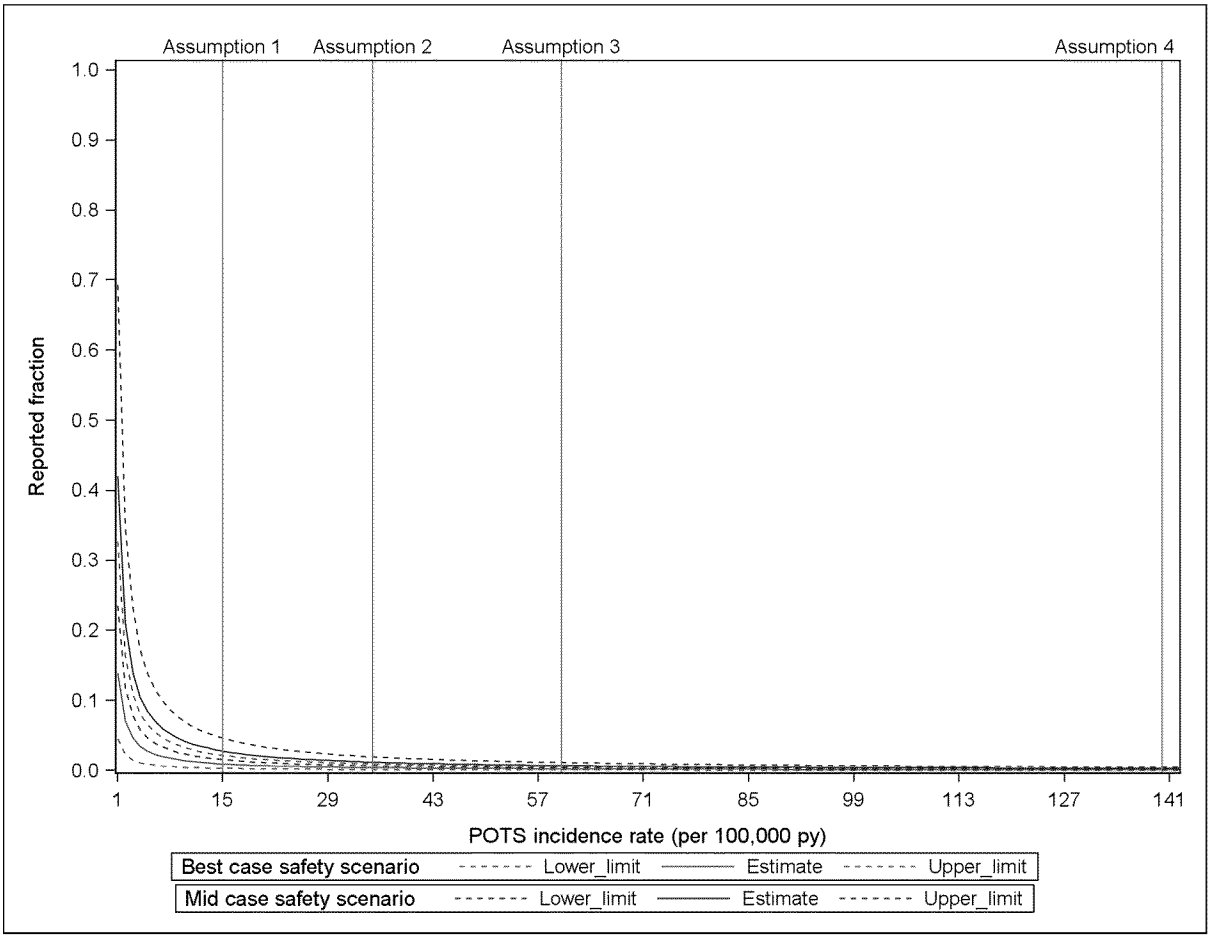
The results of the observed-to-expected analyses for worldwide data and a risk period of 1 week are presented in Figure 11 for the best-case and mid-case safety scenario. These same results for a 1 month risk period are presented in Figure 12, the 6 months risk period results are presented in Figure 13 and Figure 14 presents the results for a risk period of 1 year. For Figure 13 and Figure 14 no best-case safety scenario is presented as no confirmed cases have a TTO longer than 1 month and there would be no difference between the best and mid case scenarios.

Figure 11 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=worldwide and risk period=1 week



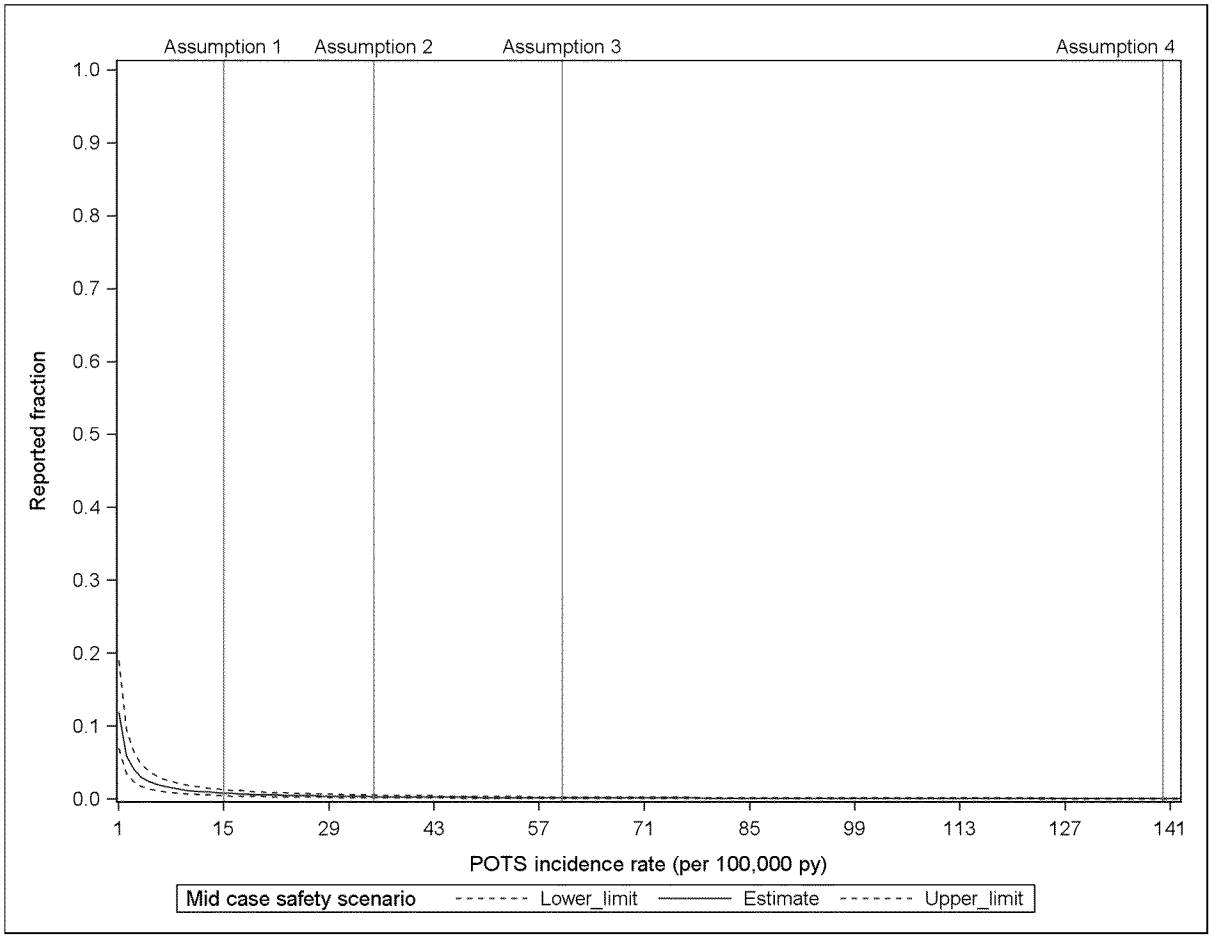
Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS worldwide and a risk period of 1 week, the observed reporting rate is equal or lower than the expected if at least 2% of the POTS cases occurring within 1 week of Cervarix vaccination were reported for the best-case 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. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 12 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=worldwide and risk period=1 month



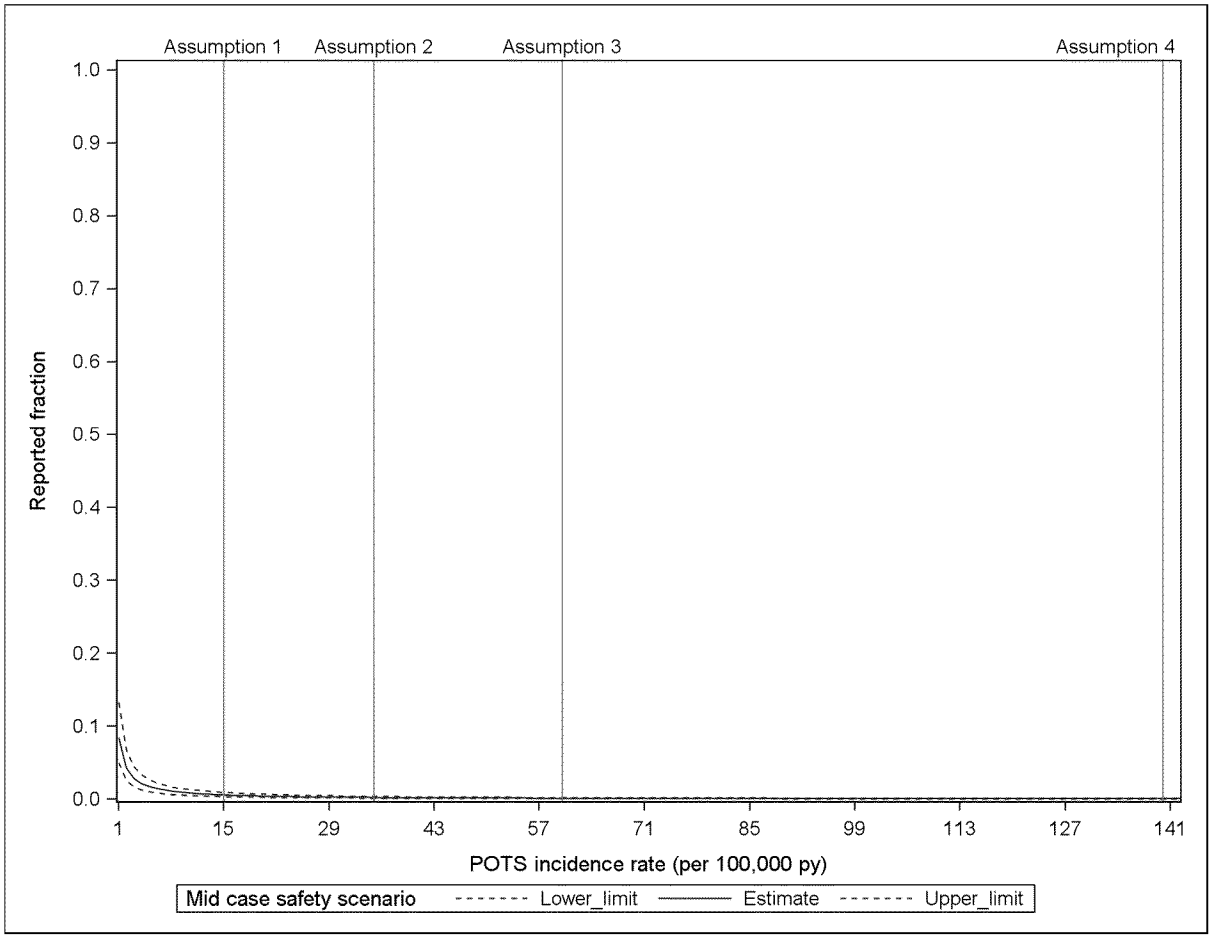
Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS worldwide and a risk period of 1 month, the observed reporting rate is equal or lower than the expected if at least 1% and 3% of the POTS cases occurring within 1 month of Cervarix vaccination were reported for the best-case and the mid-case safety scenario, respectively. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 13 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=worldwide and risk period=6 months



Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS worldwide and a risk period of 6 months, the observed reporting rate is equal or lower than the expected if at least 1% of the POTS cases occurring within 6 months of Cervarix vaccination were reported for mid-case safety scenario. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 14 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=worldwide and risk period=1 year

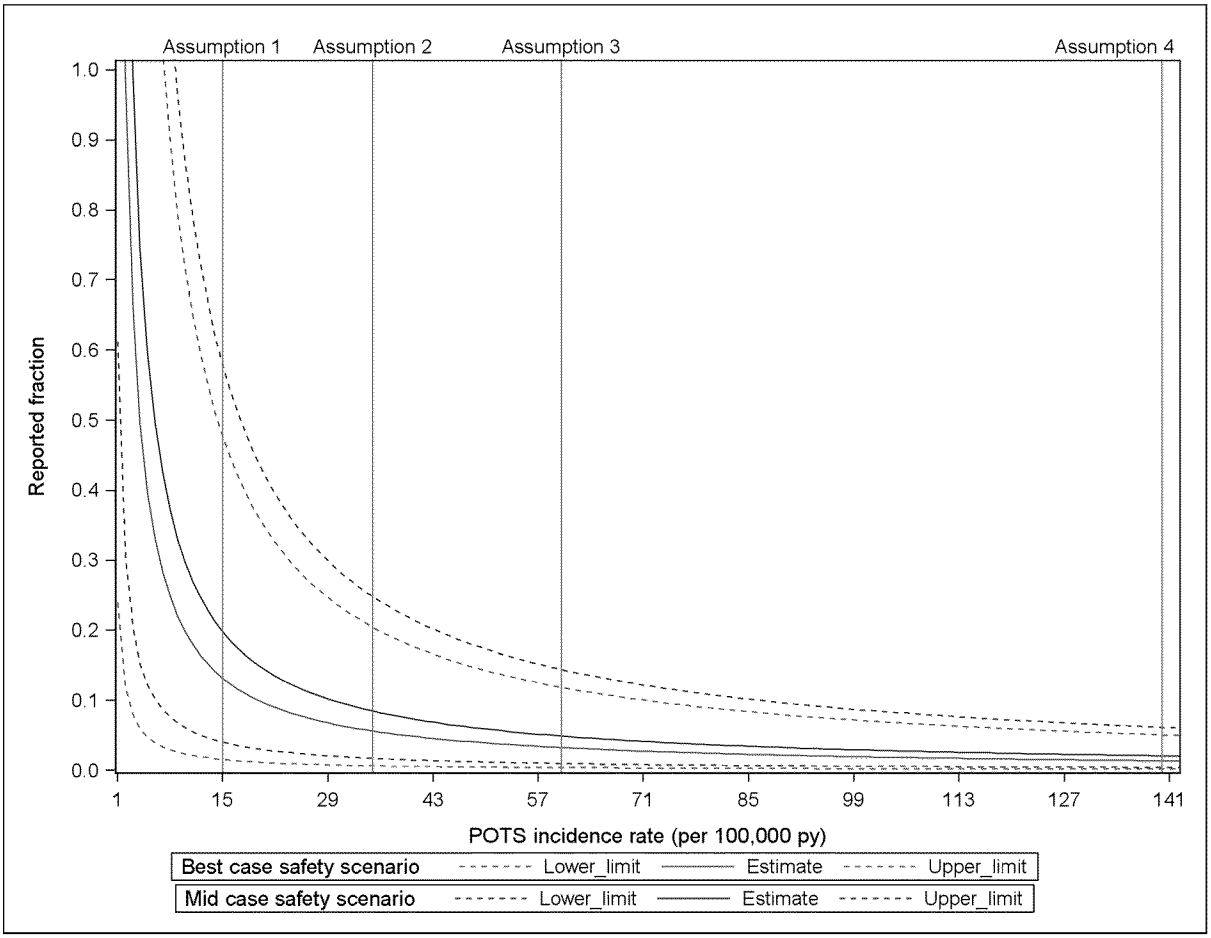


Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS worldwide and a risk period of 1 year, the observed reporting rate is equal or lower than the expected if at least 0.6% of the POTS cases occurring within 1 year of Cervarix vaccination were reported for mid-case safety scenario. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Japan

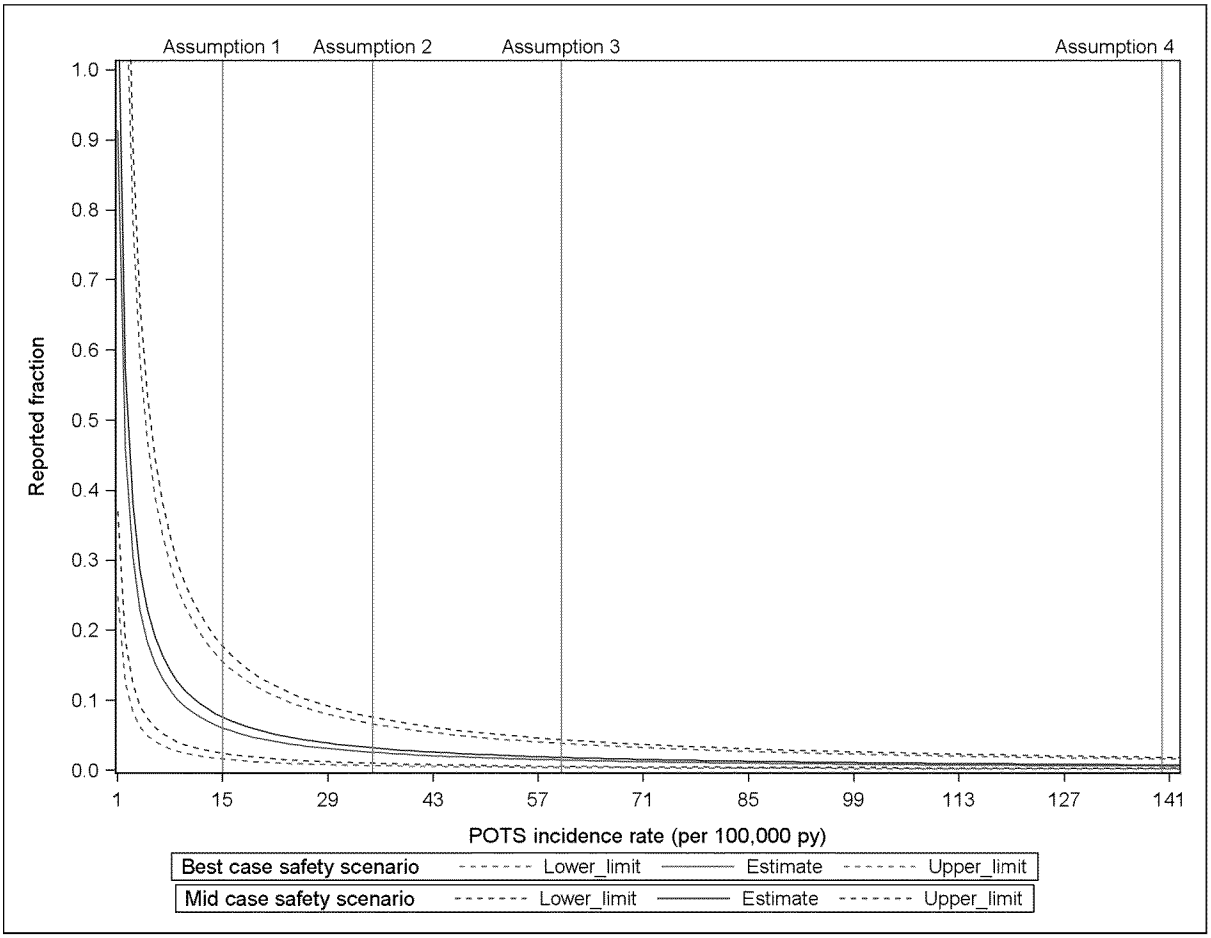
The results of the observed-to-expected analyses for Japan and a risk period of 1 week are presented in Figure 15 for the best-case and mid-case safety scenario. These same results for a 1 month risk period are presented in Figure 16, the 6 months risk period results are presented in Figure 17 and Figure 18 is presenting the results for a risk period of 1 year. For Figure 17 and no best-case scenario is presented as no confirmed cases have a TTO longer than 1 month and there would be no difference between the best and mid case scenarios.

Figure 15 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=Japan and risk period=1 week.



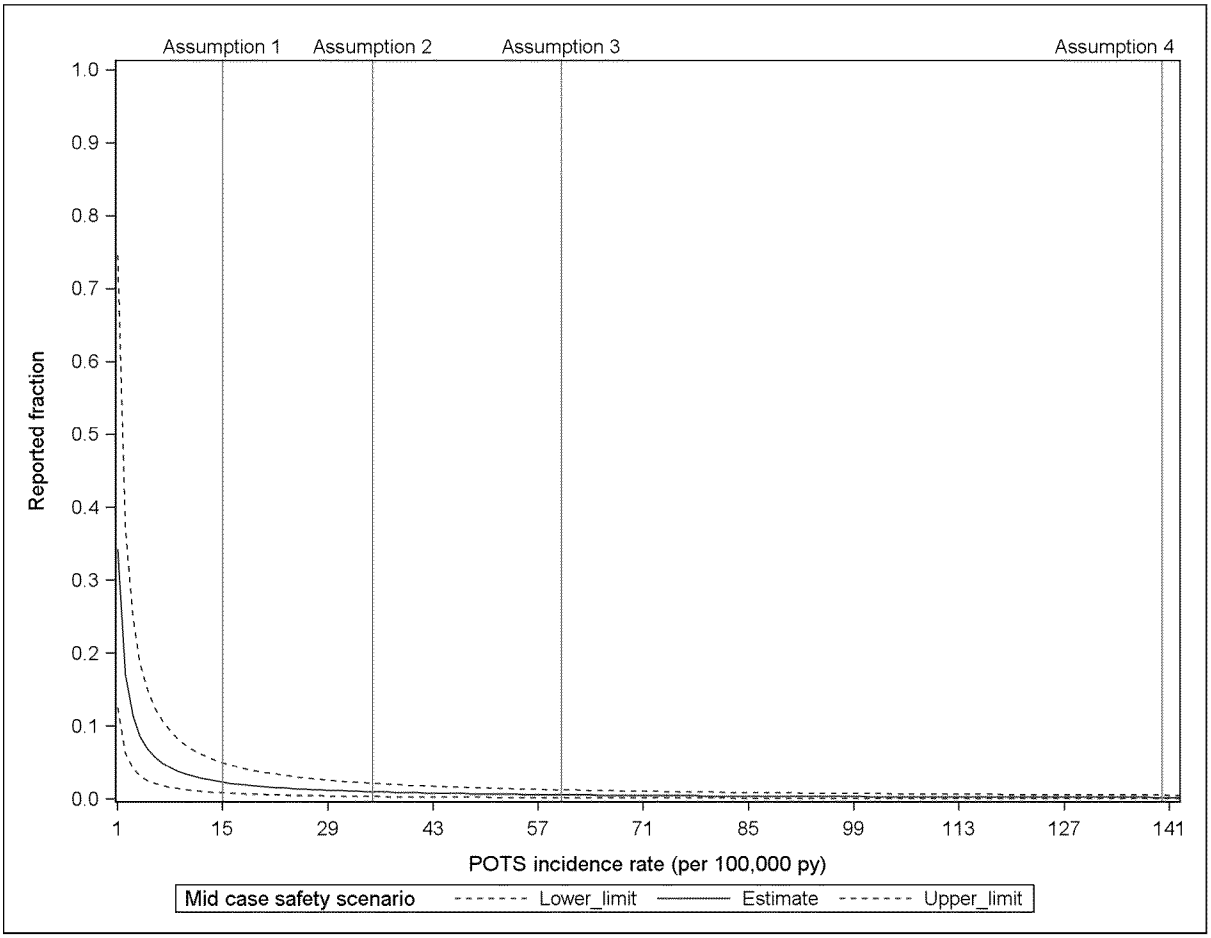
Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in Japan and a risk period of 1 week, the observed reporting rate is equal or lower than the expected if at least 13% and 20% of the POTS cases occurring within 1 week of Cervarix vaccination were reported for the best-case and the mid-case safety scenario, respectively. For the other assumptions and longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 16 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=Japan and risk period=1 month.



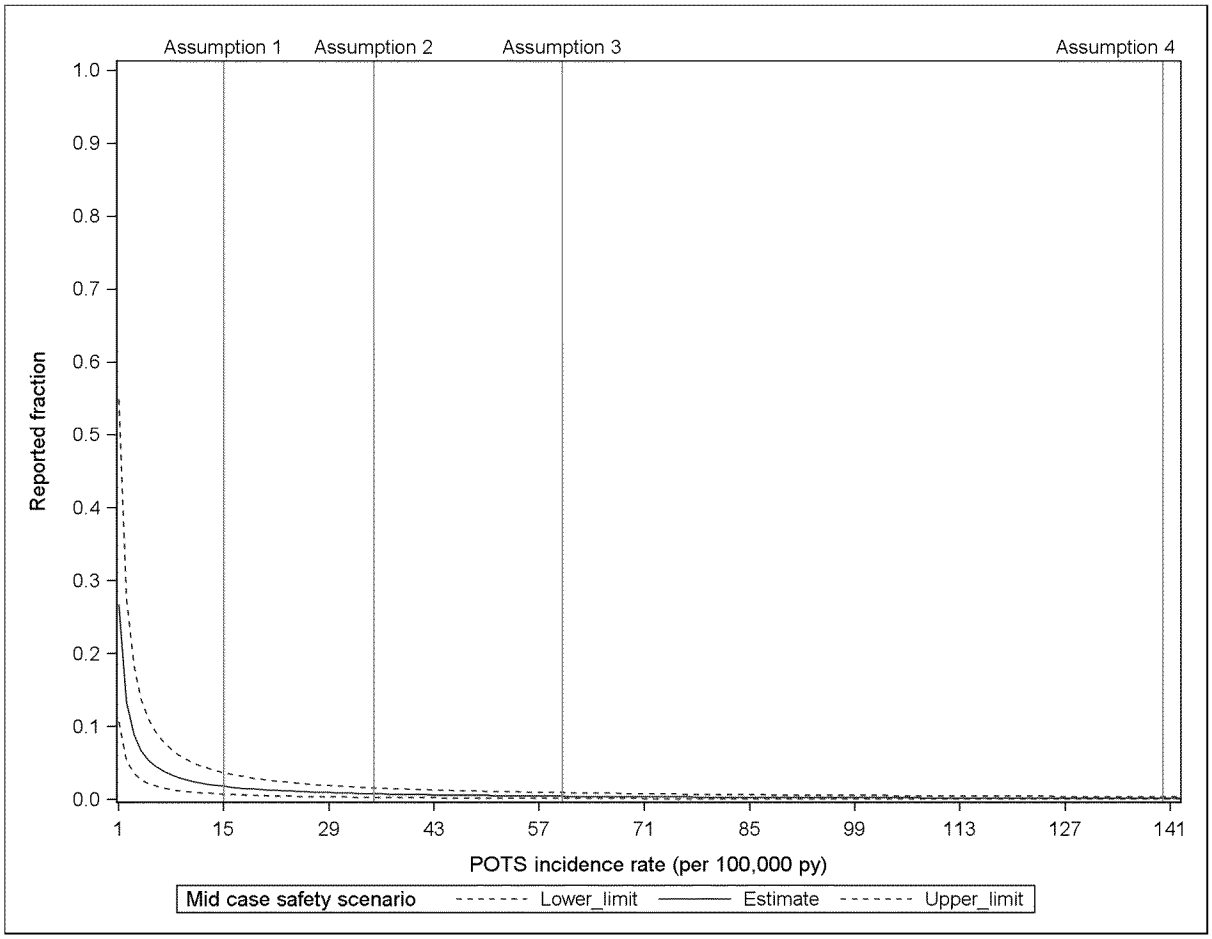
Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in Japan and a risk period of 1 month, the observed reporting rate is equal or lower than the expected if at least 6% and 8% of the POTS cases occurring within 1 month of Cervarix vaccination were reported for the best-case and the mid-case safety scenario, respectively. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 17 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=Japan and risk period=6 months.



Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in Japan and a risk period of 6 months, the observed is equal or higher than the expected if at least 2% of the POTS cases occurring within 6 months of Cervarix vaccination were reported for the mid-case safety scenario. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 18 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=Japan and risk period=1 year.

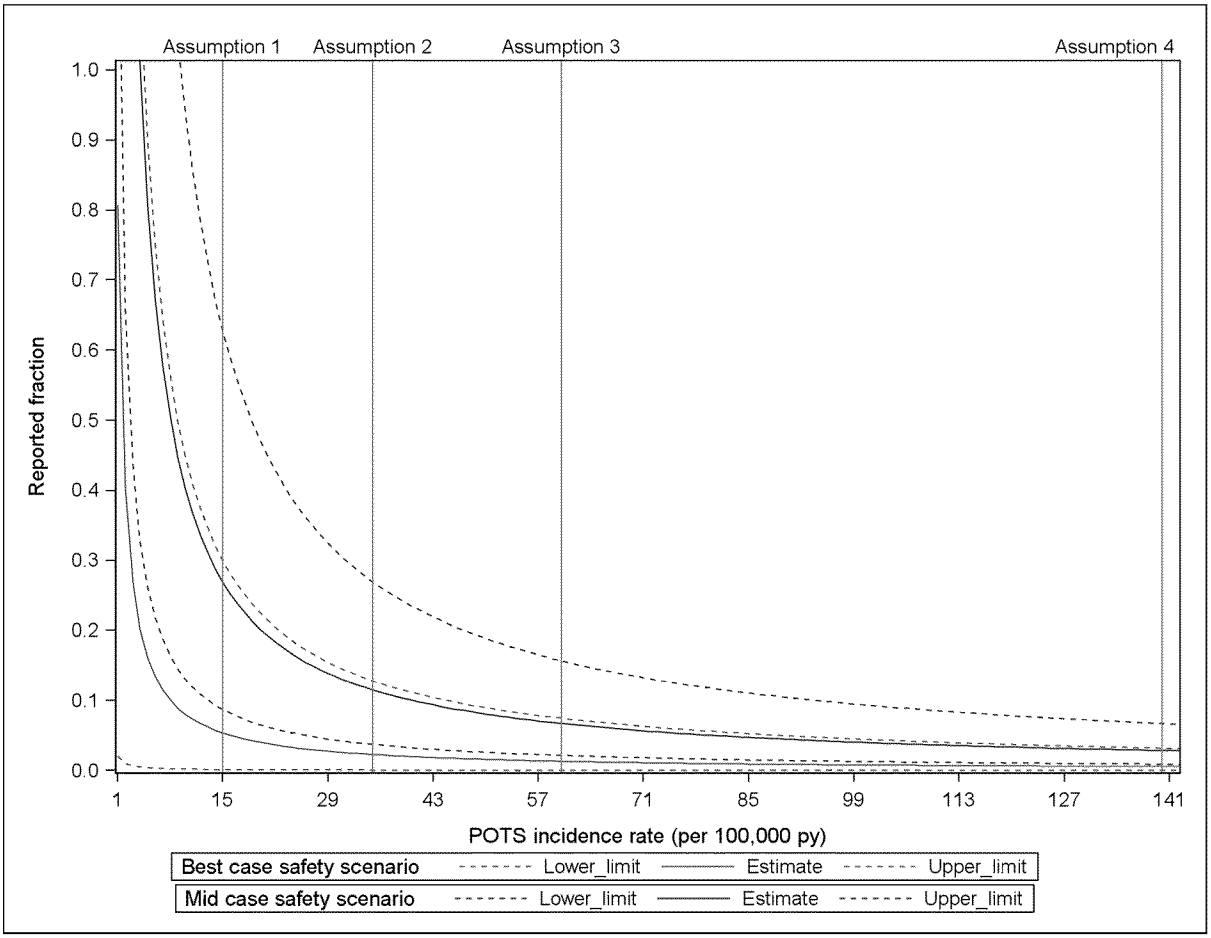


Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in Japan and a risk period of 1 year, the observed reporting rate is equal or lower than the expected if at least 1% of the POTS cases occurring within 1 year of Cervarix vaccination were reported for the mid-case safety scenario. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

United Kingdom

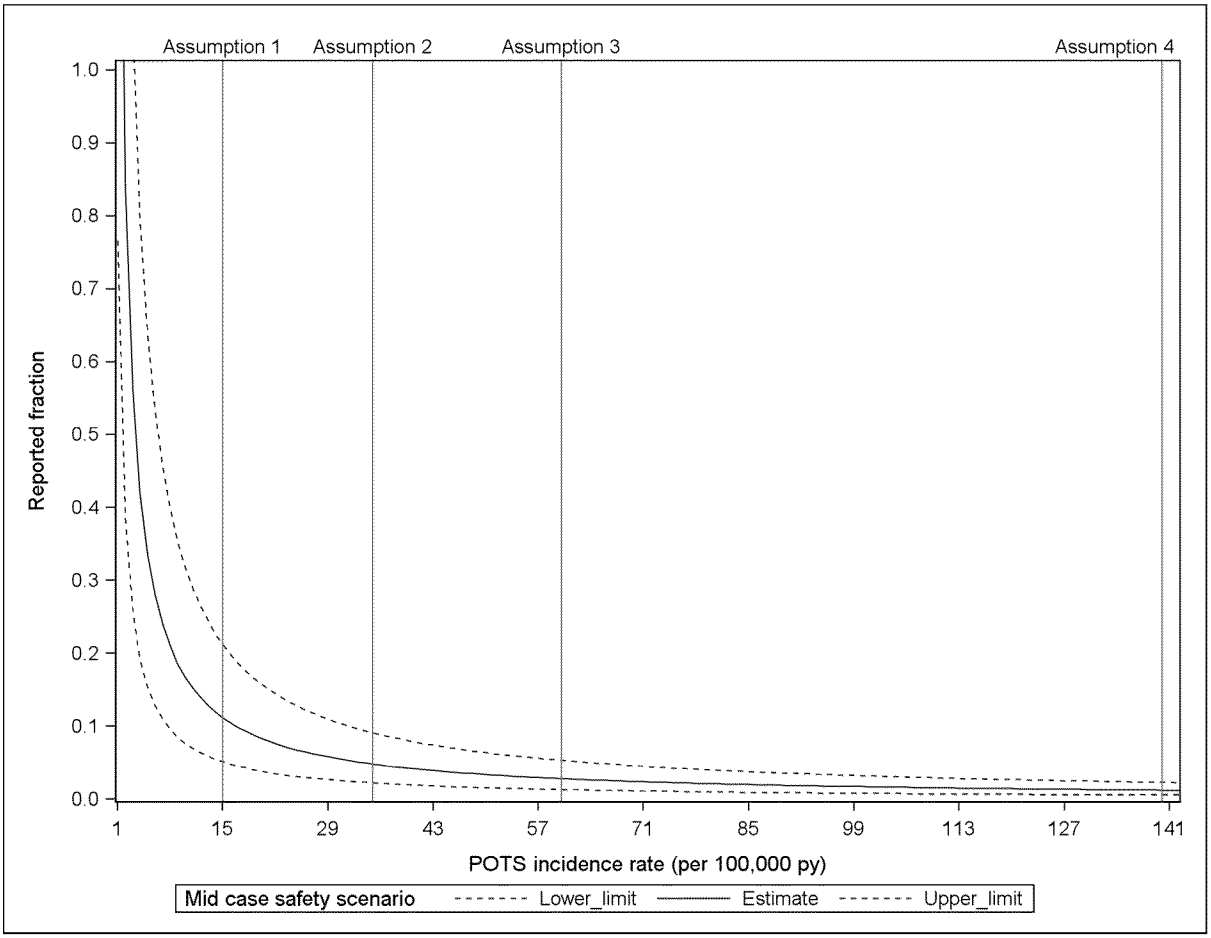
The results of the observed-to-expected analyses for UK and a risk period of 1 week are presented in figure 19 for the best-case and mid-case safety scenario. These same results for a 1 month risk period are presented in figure 20 and for the 6 months risk period results are presented in figure 21. There are no cases in the UK with a TTO longer than 6 months. For figures 20 and 21 no best-case scenario is presented as no confirmed cases have a TTO longer than 1 month and there would be no difference between the best and mid case scenarios.

Figure 19 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=UK and risk period=1 week.



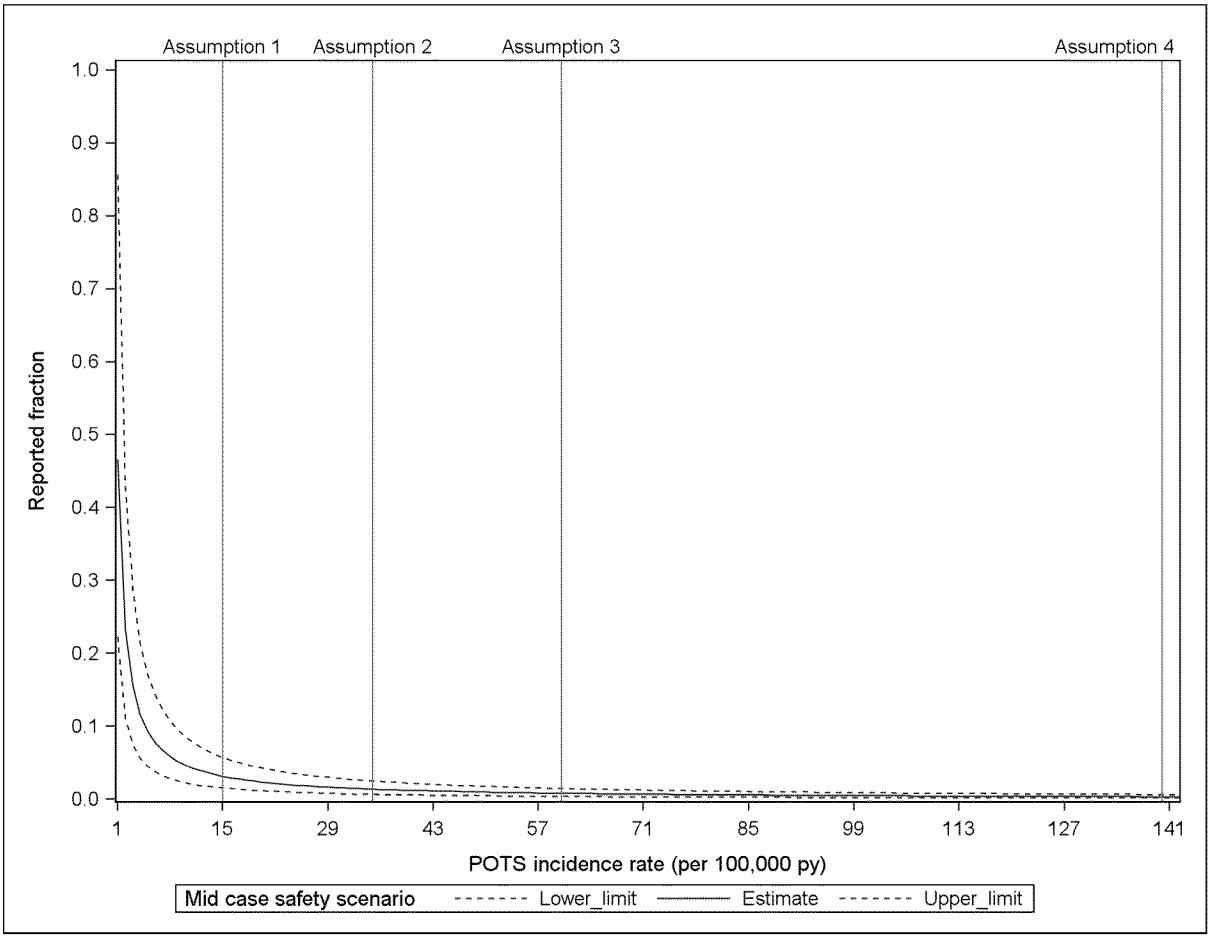
Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in the UK and a risk period of 1 week, the observed reporting rate is equal or lower than the expected if at least 5% and 27% of the POTS cases occurring within 1 week of Cervarix vaccination were reported for the best-case and the mid-case safety scenario, respectively. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 20 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=UK and risk period=1 month.



Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in the UK and a risk period of 1 month, the observed reporting rate is equal or lower than the expected if at least 11% of the POTS cases occurring within 1 month of Cervarix vaccination were reported for the mid-case safety scenario. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

Figure 21 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=UK and risk period=6 months.

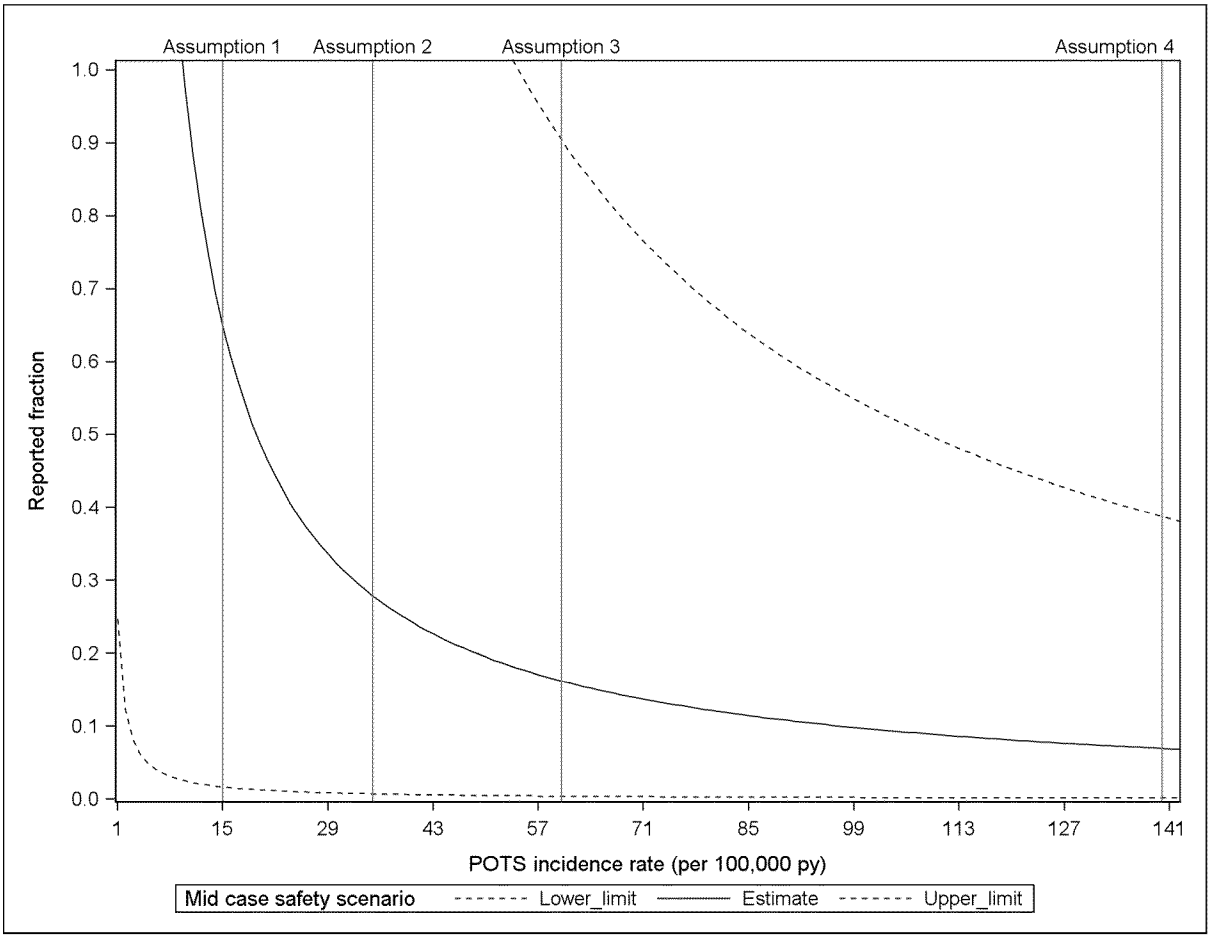


Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in the UK and a risk period of 6 months, the observed reporting rate is equal or lower than the expected if at least 3% of the POTS cases occurring within 6 months of Cervarix vaccination were reported for the mid-case safety scenario. For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

United States

The results of the observed-to-expected analyses for US and a risk period of 1 week are presented in figure 22 for mid-case safety scenario. There are no confirmed cases of POTS in the US so no best case safety scenario is presented as there would be no difference between the best and mid case scenarios. There are no cases with a TTO beyond 1 week so no figures are presented for the risk periods beyond 1 week.

Figure 22 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=US and risk period=1 week.



Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS in the US and a risk period of 1 week, the observed reporting rate is equal or lower than the expected if at least 65% of the POTS cases occurring within 1 week of Cervarix vaccination were reported for the mid-case safety scenario. 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.

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Annex 2: Background incidence rates of CRPS and POTS used for expected calculations in Observed versus Expected comparison

The calculation of expected numbers of events in the vaccinated population requires knowledge of the incidence (occurrence of new cases) of the condition in the target population. Background incidence rates for each of two conditions of interest for this request, Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS) were derived from a detailed review of the published literature.

Background incidence rates for CRPS

A literature review was conducted to identify background incidence rates of CRPS in females. Only 2 published studies of incidence rates of CRPS were identified, one from the US, one from the Netherlands. They are summarized in Table 1.

The Sandroni *et al* 2003 US study was a population-based analysis from Olmsted County, Minnesota for the period 1989-1999 (Sandroni , 2003). It has been subject to criticism, in part due to the retrospective application of CRPS diagnostic criteria to diagnoses based on clinical signs and symptoms before the criteria were published, which is thought to have been overly strict and resulted in possible underestimate of incidence rates. The de Mos *et al* 2007 study from the Netherlands was a population-based analysis of medical records from 600,000 patients throughout the Netherlands during the period 1995-2006 (de Mos , 2007). In this study, detection and validation of CRPS cases included a broad detection algorithm in the electronic medical records and diagnosis reconfirmation of potential cases through a supplemental questionnaire sent to the treating physician. In addition, fulfilment of the diagnosis according to CRPS criteria of a subset of specialist-diagnosed cases with detailed letters from specialists was conducted independently by 2 physicians and resulted in high confirmation rate of CRPS diagnosis according to the International Association for the Study of Pain (IASP) criteria. Both studies showed higher incidence rates of CRPS in females than males and an increase in incidence rates with age.

Because the Netherlands study had a superior methodological quality and was conducted more recently, incidence rates from this study were considered more reliable. In this study, the incidence rates of CRPS-1 varied between 14.9 and 121.3 per 100,000 person-years in females aged between 10-19 years and 60-69 years, respectively. These age-specific incidence rates were used as background rates for the calculation of expected numbers of CRPS, using a weighted average incidence based on the respective proportions of females in the vaccinated populations of each country/geographic region, as needed.

In summary, we used the background incidence rates of CRPS provided by de Mos (2007) for the calculation of expected numbers of CRPS. A single incidence rate assumption was used per country/geographic region, calculated as a weighted average incidence based on

the respective proportions of females in the vaccinated population of that country/geographic region, as needed.

Background prevalence rates (i.e., frequency of existing cases in the target population) are provided per EMA request, but not used in Observed vs. Expected calculations. For context, Sandroni *et al* reported on the natural history of CRPS in their Olmsted County study (Sandroni , 2003). Their main findings was that CRPS is a fairly rare condition with a high rate of spontaneous resolution, with many cases being mild and transient, and only a minority becoming chronic and severely disabled. In this study, the prevalence of CRPS was 0 and 36 per 100,000 in 10-19 and 20-29 year-old females, possibly underestimated due to the limitations mentioned above about the retrospective assessment of CRPS diagnostic criteria.

Background incidence rates for POTS

POTS is a common syndrome (Stewart , 2013) predominantly impacting females younger than 40 years old (Thieben 2007, Sidhu 2013, Agarwal 2007, Mathias 2012, Sousa 2012). Although the existence of POTS was documented decades ago (Sidhu, 2013), recognition of POTS in the medical community has increased over the past 20 years, based on work conducted at the Mayo Clinic (Rochester, MN, USA) (Schondorf , 1999). While POTS is increasingly being recognized by clinicians (Grubb , 2008), it is still an underdiagnosed and underestimated entity (Agarwal 2007, Mathias 2012, Sidhu 2013). As a result, there are minimal prevalence data for POTS in the literature, and to our knowledge, no incidence rates for POTS have been reported.

It is well established that some patients with chronic fatigue syndrome (CFS) have comorbid POTS (Reynolds 2014, Schondorf 1999, Hoad 2008, Lewis 2013, Galland 2008, Jones 2004, Oner 2014). Given the limited data on the burden of POTS and drawing upon the relationship between CFS and POTS, the MAH estimated a range of incidence rates for POTS derived from data on CFS, using the following equation

$$Incidence\ of\ POTS = \frac{(Incidence\ of\ CFS)\ *\ (\%\ CFS\ cases\ with\ POTS)}{\%\ POTS\ cases\ with\ CFS}$$

Incidence of CFS: Several studies have been published on the incidence of CFS, representing a wide range of incidence rates of CFS summarized in Table 2. Variations were mainly related to differences in diagnosis criteria and different study methods. These studies consistently show higher incidence rates of CFS in females than males. They also suggest that the incidence of CFS is higher in younger age groups. On the lower end, a study from the Netherlands reported an annual rate of 12/100,000 in 10-18 year old females, though the investigators acknowledged the rates were probably underestimated (Nijhof , 2011). A study of 18-70 year old women in Olmsted County, Minnesota, US reported a rate of 21.7 per 100,000 (Vincent , 2012), while 41/100,000 was reported for 18-64 year-old females in England (Nacul , 2011). At the upper end of the reported annual incidence rates of CFS, in a Kansas (US) study, a rate of 180 per 100,000

18-69 year-old females was reported (Reyes , 2003), a rate of 370 per 100,000 adults was reported in Scotland (Lawrie , 1997), and a rate of 950 per 100,000 in 11-12 year-old females was reported from the UK (Rimes , 2007). A recent population-based registry study by Bakken *et al* 2014 in Norway reported the incidence of CFS between 2008 and 2012 to range from approximately 50 to 65 per 100,000 person-years in 10-39 year-old females (Bakken , 2014). The incidence rates reported from this Norway study are toward the lower end of the literature estimates described above, and used robust methods. Another recent study by Donegan *et al* 2013 in the UK reported similar annual incidence rates ranging from 31 to 70 per 100,000 in 12-20 year old females (Donegan , 2013). Therefore, a range of 30 to 70 per 100,000 person-years in females 10-39 years old was used as background incidence rate of CFS.

Proportion of CFS cases with POTS: The proportion of CFS cases who have POTS has been reported in several studies summarized in Table 2. Some studies have reported proportions of 11% to 13% (Schondorf 1999, Reynolds 2014, Lewis 2013), whereas others have reported higher proportions of 25% to 42% (Freeman 1997, Galland 2008, Jones 2005, Hoad 2008). We used a range of **10% to 40%** as the proportion of CFS cases with POTS for the estimation of POTS incidence and calculation of expected numbers of POTS.

Proportion of POTS cases with CFS: While many POTS cases have fatigue, only a small fraction of POTS cases have a diagnosis of CFS. The only study providing an estimate of the proportion of POTS cases having a diagnosis of CFS was a recent study by McDonald *et al* 2014 (McDonald , 2014) that suggested a proportion of 21%. We assumed that a proportion of **20%** of incident cases of POTS also had CFS for the estimation of POTS incidence and calculation of expected numbers of POTS.

Summary estimates: In summary, we used the following assumptions for the estimation of the background incidence rates of POTS:

- CFS incidence rates of 30 to 70/100,000 person-years in 10-39 year old females
- Proportion of CFS cases with POTS: 10% to 40%
- Proportion of POTS cases with CFS: 20%

Based on the equation shown above for the calculation of POTS incidence, we obtained the following estimates for the incidence of POTS: 15, 35, 60 and 140 per 100,000 person-years in females.

In summary, the following assumptions were used for background incidence rates of POTS for the calculation of expected numbers of POTS:

- **15, 35, 60 and 140 per 100,000 person-years in females 10-39 year old**

Background prevalence rates (i.e., frequency of existing cases in the target population) are provided per EMA request, but not used in Observed vs. Expected calculations. For context, prevalence rates of POTS are unavailable but, using the same approach as for incidence, could be approximated from available prevalence rates of CFS. Prevalence rates of CFS have been

reported to range from 0.006% to 3% worldwide (Afari 2003, Ranjith 2005, Dinos 2009), mainly depending on the criteria used. A CFS prevalence of 0.2% was reported in England (Nacul, 2011). Using the same calculation as for POTS incidence based on proportion of CFS cases that have POTS (10% to 40%) and proportion of POTS that have CFS (20%), the prevalence of POTS would range approximately from 0.003% to 6%, corresponding to 3 to 6000 per 100,000.

Table 1. Publications on CRPS incidence rates (IR per 100,000 person-years)

Author, publication year	Disease	Country/Region	Study Design/Setting	Study Period	Age (years)	Females, Incidence Rate (/100,000 py)	Males, Incidence Rate (/100,000 py)
de Mos , 2007	CRPS	The Netherlands	IPCI database	1996-2005	10-19 y	14.9	1.8
					20-29 y	28.0	6.2
					30-39y	27.7	9.0
					40-49y	27.2	15.5
					50-59y	72.1	24.4
					60-69y	121.3	31.4
Sandroni , 2003	CRPS	US, Olmsted County	Mayo Clinics, medical charts review	1989-1999	10-19y	2.15	1.04
					20-29y	6.81	1.05

CRPS: Complex regional pain syndrome

Table 2. Publications on CFS incidence rates (IR per 100,000 person-years)

Author, publication year	Disease	Country/Region	Study Design/Setting	Study Period	Age (years)	Females, Incidence Rate (/100,000 py)	Males, Incidence Rate (/100,000 py)	Both genders, Incidence Rate (/100,000 py)
Gallagher , 2004	CFS/ME	UK	CPRD	1998-2001	All (8-83y)	-	-	50-55
Rimes , 2007	CFS	UK	Questionnaires	-	11-15y	-	-	1000
Nacul , 2011	CFS/ME	UK	General practices	2007-2010	18-64y	13 (6-24)	4 (1-11)	9 (5-15)
Donegan , 2013	Fatigue syndromes	UK	CPRD	2009-2011*	12-20y	40	15	-
					21+ y	-	-	55
	CFS			2008-2009	12-13y	31.2	-	-
					17-18y	69.5	-	-
				2009-2010	12-18y	47.4	-	-
				2009-2011	12-20y	32 (incident diagnosis)*	-	-
Lawrie , 1997	CFS	Scotland	Clinic, Penicuik Health Center	1991-1992	>18y	-	-	370 (40-1330)
Bakken , 2014	CFS/ME	Norway	Registry data	2008-2012	All	39.4	12.9	-
					10-14y	60*	25*	43.7
					15-19y	65*	18*	43.1
					20-24y	50*	10*	31.9
					25-29y	50*	15*	32.3
					30-34y	65*	15*	42.9
					35-39y	65*	14*	42.6
Nijhof , 2011	CFS	The Netherlands	General practices	2008-2009	10-18y	-	-	12
Minowa , 1996	CFS	Japan	Clinics	1992	All	0.51 (0.43-0.58)	0.36 (0.30-0.43)	0.46 (0.41-0.51)
Reyes , 1997	CFS	US, 4 cities	Physicians based surveillance	1989-1993	>18y	-	-	<1
Reyes , 2003	CFS	US, Kansas	Clinics	1997-2000	19-69y	-	-	180 (0-466)
Vincent , 2012	CFS	US, Olmsted Co.	Medical charts review	1998-2002	18-70y	21.74	4.39	13.16

CFS/ME: Chronic fatigue syndrome/myalgic encephalomyelitis ; * approximation

Table 3. Publications on proportion of CFS with POTS and proportion of POTS with CFS

Author, publication year	Country/Region	Study Design/Setting	Study Period	Number of subjects	Mean Age (years)	% of CFS cases with POTS	% of POTS cases with CFS
Reynolds , 2014	Australia	Hospitals	2009-2012	306	25.33	11%	-
Lewis , 2013	UK	Hospitals	2008-2011	179	40	13%	-
Hoad , 2008	UK	-	-	59	47	27%	-
Galland , 2008	New Zeland	GPs and pediatric Outpatients	-	26	Between 11-19 y	42%	-
Jones , 2005	US	-	-	10	52	30%	-
Freeman , 1997	US	Hospitals	1993-1996	20	38.9	25%	-
Schondorf , 1999	Canada	Hospitals + Specialists	1995-1996	75 (75 with CFS)	39.1	12% (9 cases with POTS)	-
McDonald , 2014	UK	Hospitals	2009-2012	136	33	-	21%

CFS: chronic fatigue syndrome ; POTS: Postural orthostatic tachycardia syndrome

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CRPS

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Question No. 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 POTS and discuss whether there is biological basis for a possible causal association.

CRPS. Complex regional pain syndrome is a chronic pain disorder that typically develops in an extremity 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 pro-inflammatory 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.,

Parvovirus B19, Campylobacter) as well as rubella and hepatitis B vaccination (De Mos 2009). 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 child-bearing 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/β-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 auto-immune 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.

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.

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Question No. 5

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

Response:

GSK has conducted different analyses 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, under-reporting 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).

Reference:

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