EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 4 November 2015
Doc. Ref: EMA/702401/2015
Confidential

Minutes and Responses to PRAC from the SAG Vaccines meeting on HPV vaccines (Article 20 referral)

(GlaxoSmithKline biologicals, Sanofi Pasteur, Merck)

21 October 2015, 9:30-15:30- Room 2F - Chair: Prof Andrew Pollard

Background

Following a request from the Pharmacovigilance Risk Assessment Committee (PRAC), a SAG vaccines meeting was convened on 21 October 2015 to provide answers to the list of questions on the above referral adopted by PRAC at their October 2015 plenary meeting.

List of participants:

- **SAG Vaccine core members**
  Margareta Blennow, Anders Lindberg, Jose Melero Elizabeth Miller, Andrew Pollard
- **Additional experts**
  Martin Ballegaard, Andreas Goebel, Max Hilz, Frank Huygen, Rolf Karlsten, Anke Luehrs, Jesper Mehlsen, Hanna Nohynek, Stefan Quasthoff (via TC), Maarten Simoons, Walter Struhal (via TC), Sara Thomas, Lill Trogstad, Massimiliano Valeriani
- **Consumer representatives**
  Sine Jensen, Maurice Vanbellinghen
- **PRAC Rapporteurs /assessors**
  Julie Williams, Qun-Ying Yue, Jean-Michel Dogne, Ulla Wandel-Liminga, [redacted].
- **CHMP Rapporteurs**
  Kristina Dunder, Daniel Brasseur
- **Observers**
  Christine Maure (WHO), Yoshihiko Sano (PMDA), Almath Spooner (PRAC), Doris Stenver (PRAC), Line Michan (PRAC)
- **EMA**
  Enrica Alteri, [redacted]

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Minutes from the SAG meeting

The meeting started at 9.30 AM and was chaired by Prof Andrew Pollard.

Declaration of Interest Statement

In preparation for the meeting any restricted involvement of members was identified taking into account the topics listed on the Agenda (see outcome of this check below). The same check was carried out for observers as well as invited experts attending either in person or via teleconference.

At the beginning of the meeting, prior to any discussion of the agenda topics, information on the involvement of members and/or experts was read out. In addition, all parties were reminded of their obligation to declare their interests (in particular any changes, omissions or errors to the already declared interests).

Outcome of the check on Declaration of Conflict of Interest

Martin Ballegaard and Rolf Karlsten had declared current financial interests and as such were only allowed to take part in discussions at the request of the Chair in the capacity of expert witness and were not allowed to take part in final conclusions of the meeting. Jesper Mehlsen and Frank Huygen had declared other relevant interests and as such were allowed to take part in the discussions but not in the final conclusions of the meeting.

Overview of the meeting

The Rapporteurs for the referral presented to the SAG an overview of the issues to be discussed, and introduced the scientific questions posed by the PRAC to the SAG vaccines. The MAHs presented their position during the open session. The meeting ended at 3.30 PM and the MAHs were briefed about the conclusions of the SAG, which will be communicated to the PRAC at their November plenary meeting.

SAG-Vaccines responses

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

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

Based on the overall considerations made by the CRPS and pain experts who studied the reports of the cases, the SAG concluded that most of the reported cases ascribed to HPV vaccines, including those from Japan, do not clearly fall into the definition of CRPS as it is currently understood using the

available diagnostic criteria. In some of the cases the available information is insufficient to make a diagnosis. In some cases discussed in the referral the long interval from vaccination to onset of symptoms (after one or two years) reduces the plausibility of an association.

POTS is a systemic syndrome which has been known for a long time under different names and is still poorly understood. POTS patients typically show persistent tachycardia for more than 10 minutes upon standing, as well as an increase in heart rate to above 120 bpm or by ≥ 30bpm, and in children and juveniles below 19 years of age by ≥ 40bpm, without arterial hypotension. A diagnosis of POTS cannot solely rely on these symptoms; other symptoms (e.g. syncope, fatigue, headaches, light-headedness, diaphoresis, tremor, palpitations, exercise intolerance, near syncope upon standing upright) vary across patients and are otherwise non-specific. Consequently, POTS seems to be defined only if given this label (i.e. a subjective syndrome), but it is otherwise not particularly well characterised. POTS overlaps with orthostatic tachycardia which occurs as a normal physiological response on standing and may be prolonged following a period of bed rest or inactivity as a result of "deconditioning". It was noted that many of the POTS cases that are part of the referral do not fit well into the typical syndrome definition, or are poorly documented or inadequately diagnosed.

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

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

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

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

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

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

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

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

The observed/expected (O/E) analysis conducted by the MAHs in the frame of the referral, and thoroughly assessed by the Rapporteurs, seems to be as robust as it could be, given the difficulties with the type of data gathered and the assumptions made. One of the difficulties mentioned was the background rates estimation; background rates seem to vary across ages and over time possibly due to changes in diagnostic criteria. Some experts considered that expected rates based on the Netherland GP data could be about 30% lower if applying Budapest criteria vs. IASP criteria, which in turn may change some of the signal calculations. However it was noted that the O/E analyses covered a range of scenarios taking into account uncertainties in both numerator and denominator, and the most plausible scenarios showed no excess of POTS or CRPS cases above the background rate considering the situation in individual countries (e.g. completeness and quality of reporting).

As far as the strength of association between HPV vaccines and POTS and CRPS is concerned, the SAG concluded that an association is not currently supported by the data, although limitations of the data, as mentioned above, must be recognised. Concerning the data that are available from the literature case series, these do not support an association both because of the lack of fit with formal definitions and because of the high risk of bias (e.g. due to lack of the necessary information to assign a diagnosis and interval to onset, or selection of cases with specific time to onset range).

In conclusion, despite the limitations of case series and passive reporting, the SAG agreed that the reports to date do no constitute a signal which would warrant further investigation by the MAH. Ongoing surveillance activities are supported in order to monitor future trends. While the SAG were of the view that the available evidence does not support a causal association, they were aware that additional work to provide further evidence would be helpful from a public health perspective to add to the data available thus far, but would be challenging for the reasons described above.

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

There was a clear view from the SAG that enhanced surveillance should continue to be performed. It was noted that there are various mechanisms to obtain information about possible reactions to drugs and vaccines and the public and the health care professionals in Europe are able to report directly.

b) If yes, then:

i. What are these characteristics:

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

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

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

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

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

In addition, the SAG considered other measures, e.g. population-based registries; the main issue identified with this approach was the risk of bias (i.e. due to enhanced consultation for the outcomes in individuals who know they are vaccinated) and the lack of consistently used diagnostic codes, which may lead to inconclusive results (though it was acknowledged that there is now a Read code for CRPS in CPRD).

Concerning the feasibility of performing studies, overall they might be feasible, despite the challenges due to the large sample size and confounders. However, concern was expressed by the SAG about the risk that studies may lead to results difficult to interpret due to bias, e.g. enhanced ascertainment of vaccinated cases due to media reporting. It was stressed that in any study the method of case ascertainment should be independent of vaccination status as preferential inclusion of vaccinated cases (selection bias) could not be dealt with by statistical methods. Several experts considered only retrospective cohort studies to be potentially of use, and that these should predate media interest.

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

If retrospective register-based studies are taken, MAHs or public health authorities should carefully consider whether the coding of conditions would adequately capture the diagnosis of POTS, CRPS and CFS, or other relevant search terms and whether there are potential sources of ascertainment bias.

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