Assessment report

Pandemrix

International non-proprietary name: pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a)

Procedure No.: EMEA/H/C/000832/II/0061

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals submitted to the European Medicines Agency on 31 August 2012 an application for a variation. This application concerns the following medicinal product:

<table>
<thead>
<tr>
<th>Medicinal product:</th>
<th>Common name:</th>
<th>Presentations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandemrix</td>
<td>pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a)</td>
<td>See Annex A</td>
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</table>

The following variation was requested:

<table>
<thead>
<tr>
<th>Variation requested</th>
<th>Type</th>
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<tbody>
<tr>
<td>C.I.z</td>
<td>II</td>
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C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation

To update the obligations related to narcolepsy currently included in Annex II of the Pandemrix MA by listing the proposed non-clinical and epidemiological studies planned to further elucidate the role of Pandemrix in the onset of narcolepsy.

The requested variation proposed amendments to the Annex II.

Rapporteur: Ian Hudson

1.2. Steps taken for the assessment

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Submission date</td>
<td>31 August 2012</td>
</tr>
<tr>
<td>Start of procedure</td>
<td>16 September 2012</td>
</tr>
<tr>
<td>Rapporteur’s preliminary assessment report circulated on</td>
<td>19 October 2012</td>
</tr>
<tr>
<td>Rapporteur’s updated assessment report circulated on</td>
<td>7 November 2012</td>
</tr>
<tr>
<td>Request for supplementary information and extension of timetable adopted by the CHMP on</td>
<td>15 November 2012</td>
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<tr>
<td>MAH’s responses submitted to the CHMP on</td>
<td>13 December 2012</td>
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<tr>
<td>Rapporteur’s preliminary assessment report on the MAH’s responses circulated on</td>
<td>28 December 2012</td>
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<tr>
<td>Rapporteur’s final assessment report on the MAH’s responses circulated on</td>
<td>9 January 2013</td>
</tr>
<tr>
<td>2nd Request for supplementary information and extension of timetable adopted by the CHMP on</td>
<td>17 January 2013</td>
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<tr>
<td>MAH’s responses submitted to the CHMP on</td>
<td>25 March 2013</td>
</tr>
<tr>
<td>Rapporteur’s preliminary assessment report on the MAH’s responses circulated on</td>
<td>30 April 2013</td>
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</tbody>
</table>
2. Scientific discussion

2.1. Introduction

Pandemrix is a split virion influenza vaccine containing A/California/7/2009 (H1N1) hemagglutinin antigen adjuvanted with AS03. AS03 is composed of squalene, DL-α-tocopherol, and polysorbate 80.

In the European Union (EU), Pandemrix containing the A/Vietnam/1194/2004 NIBRG-14 (H5N1) strain was first approved via the centralised procedure on 20 May 2008, using the ‘mock-up’ process. Upon declaration of the H1N1pdm pandemic, a variation to the original Pandemrix Marketing Authorisation (MA), to change the H5N1 strain into the pandemic A/California/7/2009 (H1N1pdm) strain, was approved in the EU under exceptional circumstances on 29 September 2009. Pandemrix was indicated for the prophylaxis of influenza in an officially declared pandemic situation, and was to be used in accordance with Official Guidance, in individuals 6 months of age and older.

On 12 August 2010, regulatory approval for the switch in the Marketing Authorization (MA) status from exceptional circumstances to a full MA was granted for Pandemrix in the EU. As a consequence, the indication changed to allow usage of Pandemrix outside of the restricted clinical setting of a pandemic situation.

On 27 August 2010, following case reports of narcolepsy after vaccination with Pandemrix mainly from Finland and Sweden, a procedure under Article 20 of Regulation (EC) No 726/2004 was initiated to assess these reports and the impact on the product’s benefit-risk balance.

On 21 July 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a final opinion in the Article 20 review procedure, based on the review of the data submitted by the MAH, as well as data available so far from epidemiological studies, an analysis of safety surveillance data, case reports from across the EU and the outcome of an expert meeting held on 12 July 2011. The CHMP concluded that the benefit-risk of Pandemrix remained positive in a restricted indication, excluding its use in persons under 20 years of age unless seasonal trivalent influenza vaccines are not available and immunisation against H1N1pdm is considered necessary.

As part of the above Article 20 procedure, the following two post-authorisation measures related to narcolepsy were included in the Pandemrix Product Information in July 2011 as conditions to the marketing authorisation:

- Conduct a retrospective cohort study, including a self-controlled case series (SCCS) analysis, in Canada (Quebec) and a follow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects (due date June 2012)
• Conduct non-clinical/c clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy (due date December 2012).

The Article 20 assessment report also commented that: ‘there is a need to consider an appropriate strategy to further evaluate the potential biological/immunological mechanisms of this association, including genetic and/or environmental contributory factors. This would allow evidence-based risk minimisation measures to be evaluated.’

Narcolepsy is now included as an identified risk in the Pandemrix RMP and is subject to close monitoring by the MAH.

In December 2011, the MAH submitted a request for Scientific Advice to seek agreement from CHMP on their proposed epidemiological and non-clinical research activities to further investigate the association between Pandemrix and narcolepsy (EMEA/H/SA/2289/1/2012/III). In February 2012, these proposals were presented by the MAH at a discussion meeting at the EMA; the final CHMP scientific advice letter was issued 15 March 2012. Although the MAH’s investigational plan was considered broadly acceptable, the CHMP commented in the Scientific Advice Procedure that "it has to be considered that even if systematic and up-to-date, the plan is basically exploratory so that if some clues are obtained they could help explain a positive association between the vaccine and narcolepsy. If nothing is found it would be more difficult to exclude that an association exists with unidentified mechanisms."

The MAH submitted this variation in order to update the specific obligations related to narcolepsy currently included in Annex II of the Pandemrix MA, by listing the proposed non-clinical and epidemiological studies (including timings for key data) planned to further elucidate the role of Pandemrix in the onset of narcolepsy. In support of the application, the MAH has provided details on the proposed investigational plans.

2.2. Non-clinical aspects

2.2.1 Proposed biological and immunological investigation plan

Background

Based on the observed strong HLA association reported for cases of narcolepsy and other supportive data including genetic polymorphism data, the MAH believes that the T cell-focused research is the most appropriate for investigation of the Pandemrix-narcolepsy association. However, the CHMP commented during the Scientific Advice procedure that "the proposal on studying mimicry and bystander, based on CD4 T cell response only, without NK and CD8 response analyses or autoantibody testing, is broadly acceptable. However, autoantibody can develop and exist in parallel with a CD4 T cell response. Testing of autoantibody may be still of value for bystander assessment, when T-cell approach is less fruitful."

Three hypotheses (non-mutually exclusive) were considered in the development of the Company’s proposed non-clinical research plan:

Mimicry

Potential similarities between H1N1 vaccine antigens/H1N1v and proteins from hypocretin-secreting neurons would lead to restimulation of pre-primed CD4 T cells. So far, no significant sequence
homology was found between the haemagglutinin (HA) and neuraminidase (NA) sequences from the H1N1 virus antigens contained in the vaccine and proteins from hypocretin-secreting neurons (hypocretin and TRIB2). Therefore, to date, analysis did not suggest any evidence for a vaccine antigen to potentially increase the risk of narcolepsy. Additional experiments are proposed to further investigate the hypothesis that molecular mimicry could play a role in the association between Pandemrix and narcolepsy.

Potential bystander activation by the AS03 adjuvant:

Immune activation induced by infection and/or vaccination could induce bystander activation of pathogenic cells. The MAH reminds that the results of investigations investigating the mode of action of AS03 (in vivo in mice and ex vivo on human cells) were reviewed in the initial Pandemrix MAA in 2007/2008, and the results have been published (Morel, 2011). The MAH has previously used these results to discuss the bystander activation hypothesis (see CHMP AR on Article 20 July 2011); specifically, the MAH comments that the data generated in mice with high dose AS03 (equivalent of ~250 human doses on weight/weight basis), indicate that AS03 improved the antigen response localised to the injection site but not distant from it. A direct inflammatory response induced by AS03, as measured by NF-kB is only detectable in muscle at the injection site, not in distant organs. In addition the MAH comments that the effect of AS03 on the enhancement of the antigen-specific antibody response was shown to be transient as demonstrated by studies using different time intervals between AS03 and antigen injection. Overall the MAH considers that these non-clinical data indicate that a systemic inflammatory effect of AS03 in humans and hence a direct impact on the brain in the particular case of narcolepsy is unlikely.

It is also discussed that assuming narcolepsy is linked to activation of T or B cells’ responses specific to host antigens, this would have to occur at the site where AS03 is inducing inflammation (muscle and draining lymph node). The MAH considers the presence of neuron-specific antigen and consequently the antigen-specific activation or reactivation of narcolepsy-associated T or B cells is unlikely in these organs. It is also considered that the theoretical risk of bystander reactivation of these cells by the local inflammatory milieu induced by AS03 is counter-balanced by the local and transient nature of the response.

Direct toxic effect or inflammation of the hypothalamus

This hypothesis concerns the theory that immune activation after infection and/or vaccination could potentially lead to an inflammatory response, leading to weakening of the blood-brain barrier and allowing access of pathogenic cells to the hypothalamus.

The MAH considers that the experiments proposed should allow for an evaluation of these hypotheses. An overview is provided in Figure 1.
Figure 1: Hypotheses to be tested through the proposed non-clinical experiments

Further details on the non-clinical experimental plan being considered by the MAH are summarised in the table below.

Table 1: Overview of proposed non-clinical research activities

<table>
<thead>
<tr>
<th>Step</th>
<th>Objective</th>
<th>Methods</th>
<th>Rational</th>
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<tbody>
<tr>
<td>Evaluation of the mimicry and bystander activation hypotheses</td>
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<tr>
<td>1A</td>
<td>To study TCRα profiles in narcoleptic patients by deep sequencing</td>
<td>Deep sequencing of CD4 TCRα repertoire in narcoleptic patients, with or without influenza vaccination.</td>
<td>To identify a potentially pathogenic CD4 T cell by sequence analysis of its TCR α chain. Using mosaic parallel &quot;deep&quot; sequencing allows analysis of the entire repertoire. A TCRα signature exclusively in patients could support the hypothesis that a pathogenic T cell clone exists.</td>
</tr>
<tr>
<td>1B</td>
<td>To assess the influenza-specificity of any TCRα signatures identified in [1A]</td>
<td>Deep sequencing of TCRα repertoire from influenza-specific CD4 T cells, after expansion of such cells by stimulation with split influenza (H1N1v).</td>
<td>To determine whether any signature identified in [1A] is influenza-specific or not. This could support either the mimicry hypothesis (influenza-specific) or the bystander hypothesis (if influenza-specific).</td>
</tr>
<tr>
<td>1C</td>
<td>To determine whether any TCRα signatures identified in [1A] are induced after vaccination with Pandemrix or non-adjuvanted H1N1v</td>
<td>Deep sequencing of CD4 TCRα repertoire in vaccines – only if a signature is found in [1A] corresponding vaccine, does the same signature exist after vaccination.</td>
<td>To determine whether vaccination in healthy subjects with some HLA could induce and expand CD4 T cell clones that can be linked to narcolepsy. If outcome is negative, the collective evidence suggests a role of pre-primed narcolepsy-specific CD4 T cells.</td>
</tr>
<tr>
<td>1D</td>
<td>To assess the influenza-specificity of any TCRα signatures identified in [1C] after vaccination with Pandemrix or non-adjuvanted H1N1v</td>
<td>Deep sequencing of TCRα repertoire from influenza-specific CD4 T cells in vaccines, after expansion of such cells by stimulation with split influenza (H1N1v). Only if positive data in [1C] can provide evidence of influenza-specificity or not. This can support either mimicry or bystander – similar to [1B].</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>To evaluate potential H1N1/human shared CD4 T cell epitopes</td>
<td>Map DQA1<em>0102/QB1</em>0602 epitopes for HANA from H1N1v and for selected proteins from hypochromic neurons. Evaluation of cross-reactive response between HANA and selected proteins from hypochromic neurons. Test phenotype of specific T cells.</td>
<td>The strict HLA-α2 of narcolepsy suggests involvement of CD4 T cells. To determine any role of molecular mimicry on the CD4 epitope level, H1N1 vaccine protein epitopes bound by the pathogenic DQA1*0602 allele will be characterised. A shared epitope between H1N1v and any protein expressed in hypochromic neurons could support the mimetic hypothesis. The high bias of CD4 T cell response in narcoleptic patients could be a key factor driving such pathogenic responses through weakening of BBB.</td>
</tr>
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</table>

BBB = Blood-brain barrier; CNS = Central nervous system; CSF = Cerebrospinal fluid; HLA = Human Leukocyte Antigen; TCRα = T-cell receptor alpha, Th = T helper cell, HA = hemagglutinin, NA = Neuraminidase.
Overview of activities to study mimicry/bystander hypotheses

To address the mimicry versus bystander question, it is proposed to work with human peripheral blood mononuclear cells (PBMC) samples (from narcolepsy patients, healthy donors and subjects who were vaccinated) and focus on CD4 T cell specificity and phenotype. Studies with human (including patient) PBMC samples would primarily serve to address whether vaccination and/or infection meets the first condition for disease (specificity).

The MAH will focus research activities on CD4 T cell responses rather than analysis of antibody responses such as testing cross-reactivity of vaccine-induced antibodies on protein from hypocretin-secreting neurons. In case the T cell approach is early terminated and cannot produce a satisfactory volume of data, the MAH states that they will consider investigating auto-antibodies as a complementary approach for evaluation of Pandemrix's bystander effect.

The MAH considers that their proposed work plan addresses the comments raised by the CHMP in the Scientific Advice:

- The original ‘bundling strategy’ in which decisions to pursue TCR sequencing analysis of specific sets of samples depended on the outcomes of earlier sequencing experiments, has been replaced by a more parallel approach.

- More samples, including samples from narcolepsy patients with a history of Pandemrix vaccination, are included in the studies.

- For epitope mimicry analysis, the MAH proposes to map DQ0602-binding peptides not only for HA and NA but also for PB1. PB1, NA and HA are the only proteins from H1N1v that are present in the reassortant viruses that are used to generate the split influenza vaccine preparations. Furthermore, and as discussed during the Scientific Advice meeting, the MAH propose to extend the analysis of cross-reactive responses to proteins from hypocretin-secreting neurons in order to study naturally processed epitopes.

Identification of a disease-specific T cell receptor signature

The MAH has provided a detailed overview of the experiments they propose to try and identify a disease-specific T cell receptor signature. The MAH proposes to identify potentially autoreactive and/or disease-associated CD4 T cells by sequence analysis of their T cell receptors, focusing on the TCRs alpha chain (TCRA), and comparing such TCRA sequencing data from narcoleptic patients with HLA-matched controls. The method to be used for this is a recent technology known as massive parallel (‘deep’) sequencing [Metzker, 2010], which will be done in collaboration with Stanford University. Deep sequencing will be performed on total CD4 T cells as well as on CD4 T cells that are stimulated with H1N1v split influenza antigens, in order to lead to an enrichment of CD4 T cells that can respond to antigens in the split virus preparation.

Regarding selection of the samples to analyse, a parallel approach is proposed, where the following sets of samples will be analysed:

1. Total CD4 T cells from DQ0602+ narcolepsy patients, with no history of Pandemrix vaccination; samples from Stanford University. HLA-matched controls. n=15/group.
2. Total CD4 T cells from DQ0602+ narcolepsy patients with history of vaccination with Pandemrix; samples from Ireland and available at Stanford. HLA-matched controls. n=20/group.
3. Total CD4 T cells from DQ0602+ healthy subjects vaccinated with Pandemrix; samples from GSK clinical study. Two time points, Day 0 and Day 21 post-vaccination. n=15/time point.
4. Total CD4 T cells from DQ0602+ healthy subjects vaccinated with non-adjuvanted H1N1v vaccine; samples from GSK clinical study. Two time points, Day 0 and Day 21 post-vaccination. n=15/time point.

Analysis of samples from groups 1 and 2 could allow identification of a narcolepsy-specific signature by comparing the TCR deep sequencing results from patient samples with control samples. Samples from groups 3 and 4 are from the clinical trial D-Pan-H1N1-AS03-033 in which safety and immunogenicity of Pandemrix and non-adjuvanted H1N1v vaccine are studied. The MAH considers that deep sequencing analysis of these samples could allow identification of TCR sequences (reflecting specific CD4 T cell clones) that expand after vaccination. These can then be compared to any specific sequences identified in narcolepsy patients.

The MAH proposes to perform TCR deep sequencing on samples that were stimulated with H1N1v split influenza virus. This aims to generate a population of CD4 T cells highly enriched for cells responding to antigenic determinants present in the H1N1v split influenza virus preparation.

Samples from narcolepsy patients with a history of Pandemrix vaccination will be used for stimulation with H1N1v split influenza and the resulting “influenza enriched” CD4 T cell pools will be used for TCR deep sequencing. If TCR deep sequencing experiments with influenza-expanded PBMC samples from narcolepsy patients yields positive results, then this approach will be extended to PBMC samples from healthy donors vaccinated with Pandemrix or non-adjuvanted H1N1v vaccine. In this case, both time points mentioned above (Day 0 and Day 21 after vaccination) will be tested in order to determine which TCR sequences are induced by the vaccination and how this depends on the adjuvant. Thus, analyses of influenza-enriched CD4 T cell pools from vaccinated healthy subjects are kept conditional on positive results from analysis of narcolepsy-associated samples. The MAH explains that the two reasons for this are:

(1) scientific (i.e. without results from narcolepsy patients it is not possible to link data from healthy subjects to disease)

(2) feasibility (i.e. large number of tests would need to be justified by positive results in the samples from narcolepsy patients, in order to demonstrate added value)

The table below presents an estimated timetable for the MAH’s experiments to identify a disease-specific T cell receptor signature.
### Table 2

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Estimated timing</th>
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<tbody>
<tr>
<td>a) Deep sequencing on CD4 T cells from narcolepsy patients (no history of Pandemrix vaccination) and HLA-matched controls (n=15/group).</td>
<td>Data expected by Dec-2012</td>
</tr>
<tr>
<td>b) Deep sequencing on CD4 T cells from narcolepsy patients (with history of Pandemrix vaccination) and HLA-matched controls (n=20/group).</td>
<td>Data expected by Sep-2013</td>
</tr>
<tr>
<td>c) Deep sequencing on CD4 T cells from subjects that received Pandemrix (Day 0 and Day 21) (n=15/time point).</td>
<td>Data expected by Dec-2013, pending re-consent of study subjects (this has been recently completed)</td>
</tr>
<tr>
<td>d) Deep sequencing on CD4 T cells from subjects that received non-adjuvanted H1N1v vaccine (Day 0 and Day 21) (n=15/time point).</td>
<td>Data expected by Dec-2013, pending re-consent of study subjects (this has been recently completed)</td>
</tr>
<tr>
<td>e) Optimisation of H1N1v split PBMC stimulation with IL-2 and IL-7.</td>
<td>Ongoing, results expected by Dec-2012</td>
</tr>
<tr>
<td>f) Deep sequencing on CD4 T cells from influenza stimulated PBMC cultures from narcolepsy patients (with history of Pandemrix vaccination) and HLA-matched controls (n=20/group).</td>
<td>Data expected by Q2-2014</td>
</tr>
<tr>
<td>g) Deep sequencing on CD4 T cells from influenza stimulated PBMC cultures from subjects that received Pandemrix (Day 0 and Day 21) (n=15/time point).</td>
<td>Data expected by Q2-2014</td>
</tr>
<tr>
<td>h) Deep sequencing on CD4 T cells from influenza stimulated PBMC cultures from subjects that received non-adjuvanted H1N1v vaccine (Day 0 and Day 21) (n=15/time point).</td>
<td>Data expected by Q2-2014</td>
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</table>

* To be done only if deep sequencing analysis of influenza expanded PBMC from narcolepsy patients yields positive results. Without such positive results, interpretation of data from vaccinated healthy donors is very difficult as there is no “disease-associated” benchmark in that situation.

Milestones a and e (see table above) have been submitted as planned in December 2012 (Pandemrix FUM 101). The MAH’s rationale for grouping milestones b), c) and d) into a single more conservative timeline (June 2014) is to allow delivering into a single document a data package that will combine the results of the deep sequencing on CD4 T cells from narcolepsy patients (with history of Pandemrix vaccination) and HLA-matched controls, deep sequencing on CD4 T cells from subjects that received Pandemrix, and deep sequencing on CD4 T cells from subjects that received non-adjuvanted H1N1v vaccine, thus allowing to concurrently discuss and interpret the data. Furthermore, the MAH explained that the feasibility check of the deep sequencing analysis (milestone a) led to the conclusion that the data analysis had to be optimised (as described in the report from Prof Mignot, submitted within FUM 101) and also that more samples have to be sequenced, from narcolepsy patients as well as from healthy vaccines. Because the originally proposed ‘bundling’ strategy was replaced by an approach in which samples from patients and healthy vaccines are sequenced without go/no go decisions, this added to the workload of the academic group that is performing the work. Hence, the proposed collective timeline for milestones b), c) and d) is considered realistic and possibly conservative.

The rationale for grouping milestones f), g) and h) into a single more conservative timeline (December 2014) is to allow sufficient time for assessment and interpretation while delivering into a single document a data package that will combine sequence data from all influenza-specific enriched CD4 T cell samples. A conservative timeline was set to allow sufficient time for achieving milestones b), c) and d); allowing six months to have the academic group perform these sequencing experiments.
Epitope mapping and peptide binding

On the basis of the strong HLA association (predisposition or protection) and TCRA polymorphism observed in narcolepsy cases, the MAH hypothesised that susceptibility to narcolepsy could be controlled by specific HLA II – TCR interactions [Hallmayer, 2009] and that peptides binding to the DQ1*0602 allele could play a role in disease. If any such pathogenic peptides are related to peptides originating from H1N1v influenza proteins and presented by this same allele, then a link between H1N1v infection and/or vaccination and narcolepsy could be envisaged. In such model, a hypocretin-neuron-derived self-peptide, when presented by the DQA1*0102/DQB1*0602 allele, could activate a specific CD4 T cell clone under certain conditions. Assuming that this specific CD4 T cell clone is crossreactive with DQA1*0102/DQB1*0602 - presented epitopes from H1N1v influenza proteins, then infection and/or vaccination could lead to expansion of such potentially pathogenic CD4 T cells. Thus, the scope of this evaluation is to identify potentially cross-reactive epitopes/determinants.

The strategy to identify potentially cross-reactive epitopes involves two different approaches, one peptide-based and one protein-based.

In summary, the MAH considers identification of cross-reactive epitopes/antigens between H1N1v and proteins from hypocretin-secreting neurons could imply that CD4 T cells specific for these epitope(s) are expanded following exposure to H1N1v influenza virus antigens. As such, this would qualify as molecular mimicry in which a pre-primed hypocretin-secreting neuron-specific CD4 T cell clone is expanded due to exposure to cross-reactive influenza epitopes. In this model, the source of influenza virus antigen could be either the vaccine or the virus itself, since the epitopes should be the same.

Whereas this model could explain the cellular and molecular specificity of the pathogenic response, the MAH considers it does not imply that expansion of such cross-reactive CD4 T cells is sufficient to trigger disease. Additional factors could be required to change a cross-reactive response into a pathogenic one. A Th17 bias of the response in narcoleptic patients could be a key factor driving such pathogenic responses.

The MAH discusses that if no positive results are found in the epitope mapping exercise, then this could mean (i) that no cross-reactive epitopes and CD4 T cells exist but a bystander effect might still be a possible mechanism or (ii) that the analysis has missed the key epitopes. This latter situation could be due to limitations in the number of selected proteins from H1N1v (HA/NA) and/or from hypocretin-secreting neurons.

It is planned to assess the CD4 T cell activation by HLA-DQ binding epitopes (by Q2- 2013), and evaluate the cross-reactive response (by end of 2013). Feasibility assessment will first need to be done with regards to presentation by HLA-DQ*0602 transfected T2 cell lines (by end of 2012). If feasibility is confirmed, a series of additional proteins of hypocretin-secreting neurons is planned to be tested. The list of proteins to be assessed is being consolidated by Prof. Mignot.

An estimated timetable for the experiments on epitope mapping and peptide binding is presented in the table below:
Milestones a), b), d) and g) (see table above), have been submitted in December 2012 within FUM 101. The MAH further clarified during the procedure that DQ0602-binding peptides have been identified for HA, NA, PB1 and hypocretin, and that Prof Mignot has established a collaboration with Dr Betsy Mellins at Stanford University, to generate T2 cells expressing DQ0602. The MAH’s rationale for grouping the other milestones into a single more conservative timeline (December 2014) is to allow delivery of a single data package that will combine the results of epitope mapping and protein analysis.

The MAH also explains that the planned use of DQ0602-expressing T2 cells as antigen-presenting cells to process candidate antigens from hypocretin neurons as a method to identify potentially cross-reactive responses is an addition as compared to the original proposal considered by the SAWP and hence has an impact on all timelines due to the impact on the workload of the group. In addition, analysis of CD4 T cells with DQ0602 tetramers was added to facilitate better analysis of potentially cross-reactive CD4 T cells.

### Evaluation of Central Nervous System inflammation/hypothalamus damage and direct toxic effect in the cotton rat

The Company hypothesises that the simple presence of self-reactive T cells may not be sufficient to trigger disease and that some CNS inflammation or disruption in the blood-brain barrier (BBB) integrity might be needed to target these responses to the hypothalamus.

As the induction of a pathogenic response is unlikely to occur in a similar way in animals, and there are no animal models that reproduce narcolepsy, the MAH propose that animal studies primarily serve to explore whether vaccination and/or infection could induce inflammation and/or damage in the CNS.

Cotton rats have been selected as the preferred animal model. The animals are sufficiently large to allow practical neurological investigations and they are susceptible to H1N1v replication.

In terms of estimated timings for results to be available, the MAH is undertaking a stepwise approach to evaluate the hypothesis of a direct toxic effect:

- **September 2013**: evaluation of potential disruption of the BBB integrity following vaccination (initially high dose) in naive or primary infected H1N1v cotton rats
- **December 2013**: evaluation of potential CNS inflammation/damage following vaccination in naïve or primary infected H1N1v cotton rats
- **June 2014**: (assuming positive results in previous steps) evaluation of immune cells infiltrated in the CNS following vaccination

Similar experiments will be conducted with low dose H1N1v vaccines (timelines not stated).

In summary, according to the MAH the cotton rat experiments are subdivided in three steps, with 3 deliverables which will be performed in a stepwise approach and that these experiments will be summarised in a single submission as proposed in Annex II with an overall due date of June 2014.

**Process and composition comparison between Pandemrix (“D-Pan”) and Arepanrix (“Q-Pan”) vaccines**

Regarding the quality comparison between Pandemrix and Arepanrix H1N1, a description of manufacturing process differences between the antigen drug substance/drug product manufactured at the Dresden, Germany and Quebec, Canada facilities, as well as a comparison of the vaccine content, were provided by the MAH.

In summary,

- With respect to antigen production, both the Q-Pan and the D-Pan processes are similar during the upstream part of the antigen production process, i.e., production and preparation of “Crude Monovalent Whole Virus Bulk”.

- Differences occur during the subsequent downstream purification process; there are five major differences between the two antigen production processes:
  - In the Q-Pan process, the crude whole virions are first UV- and formaldehyde inactivated, purified and split prior to sterile filtration. In contrast, in the D-Pan process, the crude whole virions are first purified, split and finally sodium deoxocholate- and formaldehyde-inactivated prior to sterile filtration.
  - Splitting with sodium deoxylcholate is conducted in parallel with an ultracentrifugation step in the D-Pan process, whereas in the Q-Pan process, splitting is conducted with the same agent but in batch mode.
  - The D-Pan process makes use of Tween-80 at various steps of the downstream process, whereas Tween-80 is not used in the Q-Pan process.
  - The purified inactivated, split-virion bulks are undergoing a homogenization step prior to sterile filtration in the Q-Pan process, whereas this step is not conducted for the D-Pan process.
  - Thiomersal is present in the Q-Pan process (addition during formaldehyde treatment and after the splitting step), whereas no thiomersal is added during D-Pan antigen production.
  - Although the downstream process steps sequences are different, both processes yield antigens of the same nature, i.e., purified inactivated, sterile split-virion monovalent bulk (Monovalent Bulk).

- With respect to vaccine formulation, the Q-Pan and D-Pan processes are essentially similar (Figure 2). There is only one major difference: Tween-80, triton X- 100 and magnesium chloride are used as excipients for the formulation of the D-Pan antigen drug product, whereas they are not for the formulation of the Q-Pan antigen drug product.
Comparing quality-wise the D-Pan and Q-Pan vaccines, both types of vaccines are AS03-adjuvanted, preservative-containing vaccines (5μg thiomersal/vaccine dose – 20μg thiomersal/mL in the formulated antigen vial), which contain the same amount of inactivated split-virion antigens (3.75μg/vaccine dose – 15μg HA/mL in the formulated antigen vial). The only difference resides in the presence of tween-80, triton X-100 and magnesium chloride in the D-Pan vaccines, whereas these excipients are not present in the Q-Pan vaccine (Table 4).

Table 4: Comparison of GSK Bio’s AS03 adjuvanted pandemic influenza H1N1 vaccines

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity per 0.5mL dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active ingredients</strong></td>
<td></td>
</tr>
<tr>
<td>A/California/07/2009 Inactivated Split Influenza Virions</td>
<td>3.75μg HA</td>
</tr>
<tr>
<td><strong>AS03 adjuvant System</strong></td>
<td></td>
</tr>
<tr>
<td>Squalene</td>
<td>10.69mg</td>
</tr>
<tr>
<td>DL-α-tocopherol</td>
<td>11.86mg</td>
</tr>
<tr>
<td>Polysorbate 80 (Tweens 80)</td>
<td>4.86mg</td>
</tr>
<tr>
<td><strong>Excipients</strong></td>
<td></td>
</tr>
<tr>
<td>Thimerosal</td>
<td>5μg</td>
</tr>
<tr>
<td>Sodium Chloride (NaCl)</td>
<td>3.7mg</td>
</tr>
<tr>
<td>Disodium Hydrogen Phosphate (NaHPO4)</td>
<td>0.51mg</td>
</tr>
<tr>
<td>Potassium Dihydrogen Phosphate (KHPO4)</td>
<td>0.13mg</td>
</tr>
<tr>
<td>Potassium Chloride (KCl)</td>
<td>0.05mg</td>
</tr>
<tr>
<td>Magnesium Chloride (MgCl)</td>
<td>0.012mg</td>
</tr>
<tr>
<td>Polysorbate 80 (Tweens 80)</td>
<td>2.875mg</td>
</tr>
<tr>
<td>Octanol 10 (Triton X-100)</td>
<td>3.75μg</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>ad 0.5mL</td>
</tr>
</tbody>
</table>

Abbreviation: HA, Haemaglutinin; N/A, Not applicable.

MAH Plan to investigate potential immunological differences between Pandemrix and Arepanrix

Following the outcome of the Article 5(3) procedure on the immunological differences between Pandemrix and Arepanrix, which considered a report from the Finnish THL entitled "H1N1 antigen suspension of Pandemrix and Arepanrix differ immunologically in their ability to inhibit the AS03 binding antibodies: a clue to the Pandemrix related risk of narcolepsy", the MAH was asked within this procedure to take account of the hypothesis generated in the THL’s research programme as part of the Annex II commitment.

The CHMPs further requested during the procedure that “Furthermore, if the ongoing epidemiological study in Quebec finds no evidence of an increased risk of narcolepsy following Arepanrix, or the results are inconclusive, the MAH should provide a thorough evaluation of the quality and biopharmaceutical differences considering antigens, adjuvant and any other constituents between Pandemrix and Arepanrix with a view to identifying what differences between the vaccines may have contributed to a differential risk of narcolepsy, and to further test the hypothesis generated by the THL researchers.”

The cohort and self-controlled case series data from the Quebec study have been submitted to the EMA in December 2012 as outlined further below in the section on clinical safety. According to the MAH, the rest of the analyses from the Quebec study will be released in a stepwise approach as indicated in the proposed Annex II update. The MAH considers that the availability of the test-negative case-control study results and re-analysis of the dataset with adjustment for medically-attended respiratory
infection/influenza-like illness (expected in December 2013) will allow a better position from which to conclude on the association between Arepanrix and narcolepsy. Whilst supplementary Quebec data are awaited, the MAH provided EMA/CHMP with a plan for further evaluation of the quality and biopharmaceutical differences between Pandemrix and Arepanrix during the procedure as further detailed below.

Whereas differences in antigen production process and composition between Pandemrix and Arepanrix exist, the MAH states that extrapolation of the impact of such difference on immune response is not possible given today’s understanding of immunology; in other words, immunogenicity differences cannot be predicted based on differences in production process or composition. Hence, in order to evaluate immunological differences between the two vaccines, it is essential to perform immunological measurements.

Initially, the Company proposed to determine whether there are immunological differences between Pandemrix and Arepanrix by analysing the B cell receptor (BCR) repertoires based on the rationale that the BCR repertoire, by 'looking at the antigen through the eyes of the BCR', provides an objective assessment of immunogenicity. This assessment was to be conducted in a mouse model, by 'deep sequencing' of PCR amplified BCR sequences after immunizing mice with Pandemrix or Arepanrix. This approach was challenged by the CHMP based on possible lack of power of the methodology and lack of clinical relevance of a mouse immunization model.

Therefore, the Company now proposes to further analyze samples from clinical studies in which the two vaccines were compared. In the FLU Q-PAN H1N1-AS03-045 study, children aged 3-9 years were immunized with Pandemrix or with Arepanrix and immune responses were analyzed by measuring haemagglutinin-inhibition (HI) titers. From this study, as well as from an accompanying bridging study in adults (aged 18-60 years: DPan- H1N1-017), it was concluded that both vaccines were immunologically equivalent when administered with AS03 (Launay et al, manuscript submitted for publication). In the adult study, equivalence was demonstrated in terms of HI titers at day 21 post dose 1 and at day 21 post dose 2, as well as in terms of seroconversion rates at day 21 post dose 1. In the paediatric study, equivalence was demonstrated in terms of HI titers at day 21 post vaccination. However, these conclusions were based on HI titers and/or seroconversion rates, which may have limited resolution to detect small differences. Additional analysis of samples from these studies (samples from the paediatric study in particular) by alternative methods could increase resolution of detection.

The Company proposes to use samples from the paediatric bridging study for the analysis of antibody avidity by working with the research group of Dr. Hana Golding (CBER, FDA, USA). Dr. Golding and coworkers have established a technology platform to evaluate vaccine immunogenicity using antibody avidity analysis and phage display– assisted epitope mapping. Published work from the group includes analyses of responses to MF59-adjuvanted or non-adjuvanted H5N1 and pandemic H1N1 vaccines (Khurana et al, Science Translational Medicine 2010, 2011; Khurana et al, J Infect Disease 2012). Amongst other parameters, the effects of adjuvant and age on antibody responses were analyzed. In brief, antibody avidity measurements are done using properly folded HA molecules on a ProteOn SPR (Bio-Rad) biosensor platform. In addition to antibody avidity testing, the group has mapped the antigenic targets of antibody responses using phage display technology. In this approach, phage display libraries that cover the HA and NA amino acid sequences are used to screen pooled serum samples. These studies revealed that, both for the H5N1 and the pH1N1 vaccines, the MF59 adjuvant quantitatively and qualitatively enhanced the antibody response to HA (Khurana, 2010; 2011), demonstrating the capacity of the platform to detect differences.

The proposed workplan entails the analysis of serum samples from the above-mentioned paediatric study (FLU Q-PAN H1N1-AS03-045). Avidity analysis from serum samples obtained before and at day
21 after vaccination will be tested on the ProteOn SPR platform using properly folded HA from pH1N1, according to described methods (Khurana et al, Science Translational Medicine 2011). Following analysis and interpretation of the data by the investigators, the decision will be made to proceed, or not, with phage display analysis using pooled serum samples from the same study. The go/no go decision is based on the fact that, according to the expertise from the investigators, phage display analysis is less likely to produce differentiating results if the avidity analysis does not reveal significant differences. In case of a ‘go’ decision, phage display analysis will be done using phage display libraries encompassing the HA and NA sequences, following published methods (Khurana et al, 2011). Pooled samples obtained before and at day 21 post vaccination with Pandemrix or Arepanrix will be used for the testing.

Based on this workplan, the MAH discusses that several different outcomes can be expected:

1. No differences detected by avidity. Do not proceed with phage display analysis.
2. Differences detected by avidity. Proceed with phage display analysis. No differences detected by phage display.
3. Differences detected by avidity. Proceed with phage display analysis. Differences confirmed by phage display.

The MAH discussed that scenario 1 supports immunological equivalence as demonstrated by HI titers but at a greater resolution. Scenarios 2 and 3 support the existence of immunological differences between the two vaccines. The difference between scenarios 2 and 3 is whether avidity differences translate or not into differences of the epitopes that are targeted by the antibodies. However, in these scenarios, it is not possible to link any such differences to specific components in the vaccine formulations, since the comparison is done on the two formulations, without studying contributions of individual components. The MAH also highlights that it is also not possible to link this directly to narcolepsy risks for the following reasons. First, there is no established immunological correlate of disease. Second, there were no cases of narcolepsy in the H1N1 clinical studies. Nevertheless, the more in-depth analysis as proposed is expected to contribute to the discussion on potential immunological differences. It is expected that data are generated in 2014 with a deadline for reporting in December 2014.

Dependent on the results of these ongoing studies the MAH may consider exploring pharmaceutical quality differences between Arepanrix and Pandemrix, in terms of protein content beyond HA, including neuraminidase and PB1, and measuring retained biological activity of neuraminidase.

### 2.2.1. Discussion on non-clinical aspects

The MAH has proposed conservative timelines as some of the proposals are dependent on results of previous studies and experiments which are not yet complete, and also as they plan to group as much as possible, related findings and results into the same submissions to the EMA/CHMP, which they consider will facilitate understanding and interpretation on the data. The justification is noted. It is also noted that the MAH states that significant or unexpected results would be communicated to EMA/CHMP without delay.

Of note, during the procedure the MAH GSK has submitted separately a progress report on the results of two initial components of the research agenda (Pandemrix FUM 101). One aspect of the research plan employs new "deep" sequencing technology to sequence the TCR repertoire on CD4 cells with the aim of detecting a narcolepsy-specific signature. The success of this approach relies on the sensitivity of the technique and the frequency and prevalence of corresponding T cells present in patients. The CHMP considered that initial results are encouraging and suggest
informative data can be derived from this approach; however, the results are still preliminary. Additional data will be available in September 2013 as outlined above. This milestone (with due date December 2012) can therefore be considered fulfilled and does not need to be reflected in the Annex II.

The research plan includes the deep sequencing analysis of influenza-expanded CD4 T cells from patients and controls. It is noted that data on optimisation of H1N1v PBMC stimulation with IL-2 and IL-7 were expected by December 2012 but are not provided with this update. The MAH should provide this information at the next scheduled update in Dec 2013.

A shared epitope between H1N1v and any protein expressed in hypocretin positive neurons could support the molecular mimicry hypothesis. A number of peptides in pre-pro-hypocretin that bind DQ0602 have been identified. It will be now determined whether these peptides are in fact T cell epitopes and are recognised by specific CD4 T cells. Additional studies will be needed to verify any candidate peptide is a true epitope that links a specific and pathogenic CD4 T cell response to narcolepsy and a molecular mimicry or bystander activation hypothesis.

The MAH also proposes to evaluate the potential for immunological differences between Pandemrix and their other AS03-adjuvanted H1N1 pandemic influenza vaccine, Arepanrix H1N1 in an in vivo non-clinical study using mice vaccinated with either vaccine.

The manufacturing process for the monovalent bulks can be divided into upstream and downstream steps. Differences in manufacture occur during the downstream purification process, although both processes yield antigens of the same nature. With respect to formulation of the drug product the major differences are the presence of Tween-80, Triton X-100 and magnesium chloride as excipients for the formulation of the Pandemrix antigen, whereas they are not present in the formulation of the Arepanrix antigen.

It is agreed that in order to evaluate any potential immunological differences between Pandemrix and Arepanrix, it is essential to perform immunological measurements. However, identifying clinically relevant immunological differences presents a number of challenges. The MAH’s initial plans were to nucleotide sequence and then compare the complete B cell receptor repertoires of mice vaccinated with either vaccine.

The proposed plan had several potential limitations. It seemed unlikely there would large differences in B cell receptor repertoire skewing so the observed differences in antibody sequence could be minor and hard to interpret. The proposed study would not provide any information on the antigens the antibodies were recognising. As a mouse study, confirming the relevance to humans of any immunological differences would require further studies. Finally the complexity of the deep sequencing technology meant that the study would take three years to report and data on this topic are urgently needed.

The MAH were asked to consider if alternative assays may provide an early indication of potential immunological differences. After considering the possible lack of power, unclear clinical relevance, and extended timelines of the initial plan to analyse mouse BCR repertoires, the MAH have proposed an alternative approach. The proposal is to compare antibody responses in sera samples from clinical studies in which Pandemrix and Arepanrix were directly compared. This will provide data in a more useful timeframe and could provide more meaningful information than additional animal studies at this stage.

In comparative clinical studies in children and adults immunized with both Pandemrix and Arepanrix vaccines, equivalence of antibody response was demonstrated in terms of haemagglutinin-inhibition (HI) titres and/or seroconversion rates, suggesting the two vaccines were equivalent in immune response to antigen. However, it is acknowledged simply measuring HI titres or seroconversion
rates has limited resolution to detect important immunological differences between the two vaccines and a reanalysis of these samples using more sensitive methods could be very informative.

This alternative approach will identify any differences in immunological response to the two vaccines in terms of the relative affinity for correctly folded HA and NA domains and the diversity of the HA and NA epitopes recognized. The advantage of this approach is if the two vaccines were immunologically different, particularly in the magnitude of the response, you would predict differences in antibody avidity and epitope repertoires.

The MAH proposes to use samples from the comparative paediatric study for the analysis by working with the research group of Dr. Hana Golding (CBER, FDA). This group has established a technology platform to evaluate vaccine immunogenicity using antibody avidity analysis and phage display- assisted epitope mapping. Published work from this group demonstrates the capacity of this technology to detect immunological differences between adjuvanted or non-adjuvanted H5N1 and pandemic H1N1 vaccines.

This plan represents a practical pragmatic approach to the issue that could provide useful insights.

The acknowledged weakness of this plan is that it is focused on the H1N1 antigens and not all the components of the formulation. However, this plan is more likely to shed some light on any potential immunological differences between the two vaccines, in a useful timeframe with results at least by the end of next year. The research also fits better with ongoing non-clinical studies investigating the potential roles of molecular mimicry and/or bystander activation of auto-reactive T-cells in the development of narcolepsy.

It is acknowledged that the analysis will not be able to link any observed immunological differences to narcolepsy but needs to be seen in the context of the wider studies the MAH are conducting into the root cause of narcolepsy.

The MAH have also proposed the following wording for the text to be included in the RMP as further discussed below: ‘Determine whether there are immunological differences between Pandemrix and Arepanrix H1N1 that may arise from the differential ingredients and/or from any potential differences in product quality’

Given that at this stage the root cause of narcolepsy is still being investigated and there are at present no immunological correlates of the disease this revised statement seems not unreasonable. However, it is clear the rationale for these studies remains to help the understanding of the root cause of the association of Pandemrix with narcolepsy.
2.3. **Clinical Safety aspects**

2.3.1. **Proposed epidemiological investigation plan**

**Background**

A search of the MAH’s safety database through 9 August 2012 identified 761 post-marketing case reports of narcolepsy (confirmed and unconfirmed) following vaccination with Pandemrix or Arepanrix (GSK’s other AS03-adjuvanted H1N1 pandemic vaccine, used extensively in Canada and Brazil, exposure ~59 million doses):

- 525 (69%) of these reports were received from Sweden and Finland.
- 14 reports (1.8%) were received from Canada and Brazil

There have been no reports of narcolepsy from clinical trials with AS03-adjuvanted pandemic or seasonal influenza vaccines.

The MAH provided with this submission, a summary of the main results from epidemiological studies (concerning narcolepsy): the Finnish cohort study, the Swedish case inventory study, the Irish population-based cohort study and the VAESCO case-control study. The results of these studies have been previously been assessed by the CHMP.

Table 5 presents a summary of the key results from these studies.

**Table 5:** Key results from epidemiological studies in children/adolescents in Europe (as of July 2012)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>RR (95%CI)</th>
<th>Attributable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAESCO</td>
<td>Finland</td>
<td>10.2 (1.8-Inf)</td>
<td>N/C</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>3.5 (0.4-Inf)</td>
<td>N/C</td>
</tr>
<tr>
<td></td>
<td>Signalling countries pooled (Sweden, Finland)</td>
<td>14.2 (2.5-Inf)</td>
<td>N/C</td>
</tr>
<tr>
<td></td>
<td>Non-signalling countries</td>
<td>1.6 (0.5-8.1)</td>
<td>N/C</td>
</tr>
<tr>
<td>THL</td>
<td>Finland</td>
<td>12.7 (6.1-30.8)</td>
<td>6.25</td>
</tr>
<tr>
<td>MPA</td>
<td>Sweden</td>
<td>6.6 (3.1-14.5)</td>
<td>3.6</td>
</tr>
<tr>
<td>Irish Dept of Health</td>
<td>Ireland</td>
<td>13.0 (4.8-34.7)</td>
<td>5.3</td>
</tr>
</tbody>
</table>

N/C = not calculated, RR = relative risk, CI = confidence interval

VAESCO = Vaccine Adverse Event Surveillance & Communication, THL = National Institute for Health and Welfare (Finland), MPA = Medical Products Agency (Sweden).

The MAH comments that epidemiological data available so far share similar limitations such as the inability to appropriately adjust for potential confounders, in particular influenza H1N1 infection or co-morbidities; potential selection (referral) and ascertainment biases; and potential risk of misclassification (of exposed and unexposed cases) due to the challenges of accurately determining the onset of narcolepsy symptoms. The MAH notes that the same three characteristics apply to studies conducted in Ireland, Sweden, and Finland:

- **Similar high vaccine coverage**: Pandemrix uptake in Ireland was 47.8% in children 0-4 years and 39.8% in children 5-19 years; this makes it comparable to Nordic countries where up to 70% of children were vaccinated, as opposed to other European countries with low coverage;
Similar population susceptibility to narcolepsy with high prevalence of the HLA DQB1*0602 allele (35% in Ireland, 28% in Finland, as described in the Irish and Finnish reports, respectively), as compared to lower prevalence in other European countries (e.g. 4-13% in Southern Europe);

Closeness in timing of peak influenza virus circulation and mass vaccination that was not observed in most other European countries (such as the UK).

It is discussed that despite the accumulating epidemiological data, major gaps remain in the epidemiological understanding of the association between Pandemrix and narcolepsy. In order to complement data from Europe (and in line with the commitments introduced following the Article 20 review procedure), an independent retrospective cohort study is currently ongoing in Quebec (Canada) where a similar vaccine to Pandemrix, Arepanrix (GSK’s AS03-adjuvanted H1N1 vaccine produced in the Quebec manufacturing site), was used during the 2009/2010 pandemic. The protocol and two preliminary study reports concerning this study (the Quebec study) have previously been considered by the CHMP (FUM 100). An extension to the recruitment period to June 2012 was also agreed by the CHMP, in order to allow for the inclusion of further cases.

The MAH states that the first series of final analyses (cohort design and self-controlled case series [SCCS] analysis) will be available in December 2012, in line with the first deliverable of the amended obligation.

Amendment to the Quebec study

As mentioned, the Quebec study is part of the post-authorisation measures related to narcolepsy that are included in the commitments to the Pandemrix MA. It is discussed that the strengths of the study are the availability of reliable exposure data from the provincial H1N1 immunisation registry; a thorough and blinded case ascertainment, with a strong focus on identification and confirmation of the date of symptom onset; and the overall 57% vaccine coverage in Quebec that should allow sufficient statistical power to identify exposed and unexposed cases. The MAH discusses that the initial cohort design had limitations such as a lack of adjustment for important covariate information and the absence of a true non-diseased control group.

Following the Scientific Advice procedure, the MAH proposes to further build upon the Quebec study in order to increase its robustness and generate additional data, including attempts to explore the role of infections and attempts to account for some of the biases identified in studies conducted to date. The MAH is of opinion that the proposed amendments would improve the robustness of the study and increase the likelihood to appropriately assess the association between AS03-adjuvanted H1N1v pandemic vaccine and the development of narcolepsy.

As a reminder, the current objectives of the study are:

- To describe the epidemiology and clinical phenotypic features of narcolepsy cases with onset during the period 01 January 2009 to 31 December 2010
- To assess the risk of narcolepsy following Arepanrix vaccination, using a cohort design

The study protocol is being amended with the following additional objectives:

- Conduct an additional test-negative case-control analysis to further assess any potential association between Arepanrix (as a proxy to Pandemrix) and narcolepsy, and re-assess test-negative controls after 1 year to ensure that they still represent valid controls;
- Search the Quebec provincial health insurance database system (RAM-Q) for individual information on exposure to infections as a potential confounder;
• Search for markers of previous *Streptococcus pyogenes* infection in blood samples of study subjects;

• Follow for 2 years all confirmed onset cases of narcolepsy to explore potential differences in clinical prognosis between those exposed and unexposed to Arepanrix.

The MAH considers that these additional objectives will supplement those of existing and ongoing independent research initiatives in Europe. The MAH also considers that the updated protocol will also provide an opportunity to conduct clinical follow-up of incident cases to better understand potential clinical differences in the disease course of cases exposed and unexposed to Arepanrix. The timelines are as follows:

- **December 2012**: results of cohort analysis and SCCS (including sensitivity analyses on risk periods and index dates). These data have been submitted and assessed (FU2 101.3)
- **Q2-2013**: results of test-negative case-control analysis;
- **Q3-2013**: results of additional analysis including adjustment for medically-attended respiratory infection/influenza-like illness (ILI) (RAM-Q data);
- **2013**: results of search for markers of previous *Streptococcus pyogenes* infection;
- **Q4-2014**: results of additional analysis after exclusion of controls with symptoms after 1 year of follow-up, if applicable; analysis of clinical follow-up of cases (2-year biannual follow-up).

It is stated that data will be released as they become available; however, as the study is conducted by independent investigators, it cannot be ascertained that the study will progress as indicated.

**Methods**

a) **Test-negative case-control analysis**

The test-negative design (see Figure 2) is based on the assumption that persons with EDS presenting to medical care have a similar propensity to seek care (including vaccination) without knowledge of ultimate narcolepsy diagnosis, and that narcolepsy is detected, if present, with the same likelihood regardless of vaccination status, thus minimising both referral (selection) and ascertainment biases. The MAH considers this approach ensures the comparability of cases and controls (drawn from a similar source population) on known and unknown confounder and reduces issues of selection bias. Controls will be selected from the group of patients in whom narcolepsy has been clearly ruled out.
The risk of narcolepsy associated with vaccine administration will be estimated using the odds ratio computed by conditional logistic regression.

b) Use of the Quebec provincial health insurance database system to collect covariate data

The study in China (Han, 2011) suggested that natural infection might contribute to the development of narcolepsy and these results highlighted the importance of collecting such data. However, the MAH highlights that the challenge of accurately assessing infection has been emphasised in studies in Europe and in particular by VAESCO. Proxies of exposure to infections (such as records of medically-attended respiratory infections and ILI, and childhood respiratory diseases), and data on laboratory-confirmed infection when available, will be extracted from the Quebec provincial health insurance database system (Régie de l’Assurance Maladie du Québec, RAM-Q) and used in further analyses of the Quebec dataset.

The MAH points out that in spite of the investigators’ best efforts, the assessment of influenza and other respiratory/viral infections is likely to be limited as most individuals with influenza and/or similar infections are not generally tested or recorded; in addition, proxies for such infections lack specificity. Although the test-negative case-control analysis will allow studying additional risk factors, infection-related factors that cannot be controlled for might still confound any analysis.

The request for access to medical files of cases and controls in order to obtain medical services information is ongoing; authorisation from the CAI ("Commission d’Accès à l’Information") is mandatory to obtain physician claims pertaining to patients who provided a signed authorisation to have their data accessed. Average timelines for approval are at one year at a very minimum. It is expected that these data will be available for the majority of patients in the study.

c) Search for markers of previous Streptococcus pyogenes infection

The MAH discusses that it has been shown that high titres of anti-streptolysin O (ASO) and anti-DNAse B (ADB) markers of Streptococcus pyogenes infection close to disease onset can be found in sera of narcolepsy patients, indicating that Streptococcus infection might be associated with the triggering of
the disorder, either as a cofactor, or in the context of molecular mimicry [Aran, 2009; Koepsell, 2010]. Since blood samples are collected in the Quebec study for the purpose of HLA typing, testing for these markers will be performed. The MAH points out that a potential limitation of this assessment is that because the decay in antibody titres with respect to onset and progression of disease is unknown, the absence of antibody titres might not conclusively exclude an antecedent infection (i.e. it has a low negative predictive value). However, a number of recent narcolepsy cases in Quebec had blood samples taken at the time of disease evaluation, before the present study was implemented; testing will be performed for available stored sera as well as for new samples collected for the purpose of the study.

d) Follow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated versus non-vaccinated subjects

The MAH states that cases included in the study will be followed for two years to explore potential differences in clinical prognosis between those exposed and unexposed to Arepanrix. In addition to the routine regular clinical interview, a systematic evaluation will be performed using a series of instruments including the Epworth Sleepiness Scale and the Medical Outcome Study Short Form-36 (MOS – SF-36 Questionnaire).

Additional information on epidemiological plans

Regarding additional CHMP comments on epidemiological aspects of the MAH’s proposal for further research (made during the SA procedure), specifically on modelling of pandemic viral infection, time of vaccination and the relation of these to onset of disease, the MAH states that they have started developing a project to quantify the number of children potentially exposed to natural H1N1 infection prior to vaccination, using mathematical modelling to estimate:

- The proportion of individuals already infected (symptomatic and asymptomatic) at the time of vaccination, by pandemic week and age group;
- If possible, the distribution of the time since H1N1 infection for those individuals already infected, by pandemic week and by age group.

Candidate countries currently being evaluated for this analysis are Norway, Finland, Canada (Quebec) and the UK. The MAH is currently evaluating the most appropriate countries/regions, based on availability of data needed to input the model (including but not limited to: age- and country or region-stratified H1N1 seroprevalence before, during, and after the pandemic, age- and country or region-stratified surveillance reports of H1N1 infection, contact pattern data, vaccine effectiveness, age- and country or region-stratified vaccine uptake by age and week, use of antivirals). Country or region-specific deterministic compartmental transmission models of H1N1 spread, stratified by age, using a common model structure and common assumptions about H1N1’s natural history, will be developed.

A protocol outline has been submitted. The proposed timelines are as follows:

- First phase: evaluation in one country or region (Q1-2013)
- Second phase to be confirmed, based on availability of data: extend to one additional country (to be further determined)

During the procedure, the MAH explained that it is foreseen to group some of the deliverables in ‘packages’ to facilitate analysis and interpretation of related research topics (further justification is provided below).
Therefore the MAH has proposed to provide CHMP with data packages at four time points (i.e. December 2012, December 2013, June 2014 and December 2014. However, the MAH indicates that significant or unexpected results would be communicated without delay.

Proposed epidemiological investigational plan

It is explained that the rational for grouping the additional Quebec analyses into more conservative timelines (Q4 2013 to Q4 2014) is to allow delivering a data package that will combine the results of additional analyses of the Quebec study into a single document, thus allowing the concurrent discussion and interpretation of the data. The MAH considers that this will also allow anticipating possible challenges in the recruitment of controls and delays in the access to RAM-Q files:

- Recruitment of controls is still ongoing and the investigators have not yet communicated a date at which they think a sufficient number of controls will have been enrolled; in addition, ethical approval for the recruitment of paediatric controls from Sainte-Justine hospital is still pending.
- The request to obtain information on medical visits of cases and controls from the Quebec Health Insurance Board was transmitted by the investigators to the Quebec Information Access Commission (Commission d’Accès à l’Information du Québec) on September 10th 2012. The investigators highlighted that it can take up to 15 months to be granted access; it then takes an additional 1-2 months to obtain the data.
- Finally, the MAH highlights that delays have been experienced in previous deliverables from Quebec, despite timelines pre-agreed with the investigators.

2.3.2. Discussion on clinical safety aspects

Overall, the CHMP agreed to the proposed timelines concerning the Quebec study. It should however be noted that the data package submitted in December 2012 (FU2 100.3) showed that the results were inconclusive regarding the relationship between Pandemrix and narcolepsy and that based on the results presented so far, it is likely that an increased risk of narcolepsy of the same magnitude as that observed for Pandemrix in Europe, can be excluded for Arepanrix. As proposed, additional data from this study are expected by the end of 2013. The milestone with due date December 2012 related to the above data package from the Quebec study can however be considered fulfilled and does not need to be reflected in the Annex II.

The MAH’s proposal to use mathematical modelling to quantify the number of children potentially exposed to natural H1N1 infection prior to vaccination is noted. However, this additional work is outside the specific scope of the Annex II commitments.

2.4. Risk management plan

The MAH has provided an updated RMP according to the new template which reflects as a Pharmacovigilance action for the safety concern of narcolepsy, their commitment to evaluating the potential for immunological differences between Pandemrix and Arepanrix.
2.4.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The non-clinical section of the safety specification has been revised to reflect the MAH's updated proposal for investigating immunological differences between Pandemrix and Arepanrix as discussed in the variation procedure II/61 (this is subject to CHMP approval). Other sections of the RMP which have been updated include the pharmacovigilance plan, risk minimisation plan and lay summary of the RMP.

The RMP sections: safety specification, pharmacovigilance plan, risk minimisation measures and RMP summary are acceptable and the PRAC considers that the RMP can be considered approvable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Ongoing studies to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy was considered as missing information.

The MAH has now included in the section on non-clinical studies to evaluate a signal for narcolepsy that they plan to evaluate the potential immunological differences between Pandemrix and Arepanrix H1N1. This is also included in the summary of safety concerns from non-clinical data.

Table 2 of the non-clinical section has also been revised to reflect the MAH's revised plan to investigate the immunological differences between Pandemrix and Arepanrix as per the 3rd RSI response to variation II/61 (circulated 11/07/2013).

There are no other noteworthy changes to the non-clinical section of the safety specification.

Following revision of the non-clinical investigation plan to include additional proposals to investigate immunological differences between Pandemrix and Arepanrix, the updates to the non-clinical section of the RMP safety specification are considered acceptable.

Pharmacovigilance plans

Enhanced passive surveillance is conducted for: anaphylaxis, Bell's palsy, convulsion, demyelinating disorders, encephalitis, Guillain-Barré syndrome, neuritis, vasculitis, and vaccination failure. Close monitoring is also performed for autoimmune hepatitis, increased aminotransferase concentrations, narcolepsy, and solid organ transplant rejection. The MAH uses targeted questionnaires to maximise consistent documentation of case reports.

As per the new RMP template, the MAH has included tables summarising the identified and potential safety concerns and overview of Pharmacovigilance actions. For brevity, only the tables where new information is presented are included in this report:
<table>
<thead>
<tr>
<th>Areas requiring confirmation or further investigation</th>
<th>Routine and additional PhV activities</th>
<th>Objectives</th>
</tr>
</thead>
</table>
| Elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy | • Conduct feasibility assessment of deep sequencing of CD4 T cells from narcoleptic patients. If deep sequencing approach is proven feasible:  
  • identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccinees  
  • if identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients  
  • Identify DQ*0602 binding peptides from haemagglutinin, neuraminidase, PB1, and hypocretin  
  • Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*0602 binders and with additional proteins using T2 cells as antigen-presenting cells  
  • Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain barrier integrity and central nervous system inflammation/damage. | • To identify a potentially pathogenic CD4 T cell by sequence analysis of its T cell receptor alpha (TCRA). Using massive parallel ('deep') sequencing allows analysis of the entire repertoire. A TCRA signature exclusively in patients could support the hypothesis that a pathogenic T cell clone exists.  
• To determine whether any TCRA signature identified is influenza-specific or not. This could support either the mimicry hypothesis (if influenza-specific) or the bystander hypothesis (if not influenza-specific).  
• To determine whether vaccination in healthy subjects with same HLA could induce/expand CD4 T cell clones that can be linked to narcolepsy. If outcome is negative, the collective evidence suggests a role of pre-primed narcolepsy-specific CD4 T cells.  
• If CD4 T cell clones can be linked to narcolepsy, then to determine whether such TCRA signature+ cells are influenza-specific or not.  
• The strict HLA-link of narcolepsy suggests involvement of CD4 T cells. To determine any role of molecular mimicry on the CD4 epitope level, H1N1 vaccine protein epitopes bound by the pathogenic DQB1*0602 allele will be characterised. A shared epitope between H1N1v and any protein expressed in hypocretin+ neurons could support the mimicry hypothesis.  
• Th17 bias of CD4 T cell response in narcoleptic patients could be a key factor driving such
### Narcolepsy (identified risk)

<table>
<thead>
<tr>
<th>Determine whether there are immunological differences between Pandemrix and Arepanrix H1N1 that may arise from the differential ingredients and/or from any potential differences in product quality</th>
<th>Use samples from the paediatric bridging study (Q-Pan H1N1-045) for the analysis of antibody avidity and phage display-assisted epitope mapping.</th>
<th>To determine whether vaccination has any effect on the central nervous system (CNS), based on the assumption that to explain a putative vaccine effect on narcolepsy, it seems plausible that there should be a CNS impact. Whereas it is not expected that narcolepsy is seen in this model, it could be seen whether the condition of CNS invasion/blood-brain barrier integrity disruption is met.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine if there is an increased risk of narcolepsy following vaccination with Arepanrix H1N1</td>
<td>Conduct a retrospective cohort study, including nested self-controlled case series and test-negative case-control analyses, in Canada (Québec) and a follow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated versus non-vaccinated subjects</td>
<td>To evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 based on the assumption that antibody avidity measurement and phage display assisted epitope mapping are the most appropriate method to increase resolution of detection of differences.</td>
</tr>
</tbody>
</table>

### Solid organ transplant rejection (potential risk)

<table>
<thead>
<tr>
<th>Areas requiring confirmation or further investigation</th>
<th>Routine and additional PhV activities</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine whether there is an increased risk of solid organ transplant rejection following vaccination with Pandemrix</td>
<td>Enhanced pharmacovigilance during a pandemic:  - Weekly signal detection  - Individual reports expedited to regulators  - Cumulative analysis included in full PSUR following end of pandemic period</td>
<td>To determine whether there is an increased risk of solid organ transplant rejection.</td>
</tr>
</tbody>
</table>
### Solid organ transplant rejection (potential risk)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduct a retrospective, observational, self-controlled case series analysis in the UK Clinical Practice Research Datalink GP Online Database to estimate the risk of solid organ transplant rejection following vaccination with Pandemrix</td>
<td>To determine whether there is an increased risk of solid organ transplant rejection.</td>
</tr>
<tr>
<td>Assess feasibility of conducting an additional observational study involving primary data collection</td>
<td>To determine whether there is an increased risk of solid organ transplant rejection.</td>
</tr>
</tbody>
</table>
| Enhanced pharmacovigilance outside a declared pandemic:  
  - Monthly signal detection  
  - Individual reports expedited to regulators  
  - Close monitoring in PSURs | Enhanced pharmacovigilance outside a declared pandemic:  
  - Monthly signal detection  
  - Individual reports expedited to regulators  
  - Close monitoring in PSURs |

Details of the MAH’s narcolepsy research program have been included as Pharmacovigilance actions for the identified risk of narcolepsy. As requested, the MAH has included as a Pharmacovigilance activity to address the risk of narcolepsy, their commitment to investigating whether there are immunological differences between Pandemrix and Arepanrix H1N1. This has been revised in RMPv16 to reflect the MAH’s revised proposal and timelines for investigating this issue.

The MAH has proposed some revised wording for the title of the investigation area focusing on immunological differences between Pandemrix and Arepanrix.

The additional analyses in the Quebec narcolepsy study with Arepanrix H1N1, as proposed in the Scientific Advice procedure (March 2012) has also been reflected in the PhV plan.

A description of the MAH’s ongoing SCCS analysis on the risk of transplant rejection has been included as a Pharmacovigilance activity for this potential risk.

### Risk minimisation measures

**Summary of the risk minimisation measures**

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever in children</td>
<td>The labelling contains a warning/precaution regarding increased risk of fever following the second dose of vaccine in children 6 to 35 months of age. The labelling recommends monitoring of temperature and measures to lower the fever (such as antipyretic medication as seems clinically necessary) are recommended in young children (e.g. up to approximately 6 years of age) after each dose of Pandemrix.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>The indication in the EU SmPC was amended to indicate that Pandemrix should be used in persons under the age of 20 years only if seasonal trivalent influenza vaccine is not available and immunisation against (H1N1)v is considered necessary. The EU SmPC contains information regarding available data from epidemiological studies in the <strong>Special warnings and precautions for use</strong> section. Narcolepsy with or without cataplexy is listed in the <strong>Undesirable effects</strong> section of the EU SmPC.</td>
<td>None</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>The labelling contains a contraindication to the use of Pandemrix in persons with known anaphylaxis following exposure to any of the constituents or trace residues of the vaccine. The labelling contains a precaution regarding the use of Pandemrix in persons with known hypersensitivity, other than anaphylaxis, to vaccine constituents, excipients, or residues.</td>
<td>None</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Convulsion</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Demyelinating disorders</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Increased concentrations of hepatic enzymes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Neuritis</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Vaccination failure</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Vaccine effectiveness</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Limited data in subjects with compensated</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| underlying conditions; No data in subjects with severe  | The package leaflet and the **Use and Handling** section of the SmPC provide detailed instructions for mixing the vaccine; the labelling of the vials has been designed in order to enable easy distinction between the antigen vial and the adjuvant vial. | 1: Provide stand-alone instructional materials (pictograms and a video) that demonstrate proper mixing to governments who purchase the vaccine.  
2: Provide stickers in each package of vaccine that include the vaccine brand name and batch number; the stickers can be affixed to the healthcare records of the vaccine recipients or other document that governments used to record the identity of vaccine recipients. |
| underlying conditions and immunocompromise              |                                                                                                      |                                                                                                      |
| Medical errors/ misidentification of vaccine            |                                                                                                      |                                                                                                      |
| Contamination of multiple-dose vials                    | The package leaflet and the **Use and Handling** section of the SmPC provide detailed instructions for mixing and administration of the vaccine with instructions to discard the vaccine for any variation in appearance and to replace the needle used for withdrawal of vaccine with a needle suitable for intramuscular injection. **Shelf-Life** section of the SmPC states, "After mixing, the vaccine should be used within one working day." Vaccine contains thiomersal as a preservative. | Provide stand-alone instructional materials (pictograms and a video) that demonstrate proper mixing and administration of vaccine to governments who purchase the vaccine. |
| Coring of the rubber stopper on the antigen vial        | The package leaflet and the **Use and Handling** section of the SmPC instruct vaccine providers to bring the adjuvant and antigen vials to | Provide to healthcare providers a Question & Answer document that includes the instruction to bring the adjuvant and |

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Safety concern | Routine risk minimisation measures | Additional risk minimisation measures
---|---|---
| room temperature prior to mixing. | antigen vials to room temperature prior to mixing | 

Solid organ transplant rejection | None | None

Based on the information in the last PSUR and the updates to the current RMP version, no further changes to the current risk minimisation activities are required.

The CHMP endorsed this advice without changes.

### 2.5. Changes to the Product Information

Annex II of the Product Information was updated as follows:

- **Obligation to conduct post-authorisation measures**

- **OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the below following measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduct a retrospective epidemiological cohort study, including a self-controlled case series (SCCS) analysis, in Canada (Quebec) and a-fallow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects; - Test-negative case-control study results - Re-analysis of the dataset with adjustment for medically-attended respiratory infection/influenza-like illness - Re-analysis of the dataset after exclusion of symptomatic controls, after 1 year follow-up (if applicable); and description of the clinical follow-up of cases for 2 years.</td>
<td>December 2012 December 2013 December 2013 December 2014</td>
</tr>
</tbody>
</table>
Conduct non-clinical/clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy:
- If deep sequencing approach is proven feasible:
  - Identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccinees
  - If identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients
- Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*0602 binders and with additional proteins using T2 cells as antigen-presenting cells
- Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage.
- Evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared.

During the procedure, the CHMP requested further amendments to the initially proposed Annexes as discussed in detail above.

Changes were also made to the PI to bring it in line with the current QRD template, which were accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Czech Republic, Croatia, Cyprus and Poland.

3. Overall conclusion and impact on the benefit/risk balance

The MAH has submitted this application for a type II variation to update the specific obligations concerning the safety signal of narcolepsy which were introduced to Annex II of the product information at the conclusion of the Article 20 referral procedure in July 2011.

- Conduct a retrospective cohort study, including a self-controlled case series (SCCS) analysis, in Canada (Quebec) and a follow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects (due date June 2012)
- Conduct non-clinical/clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy (due date December 2012).

The first series of final analyses (cohort design and self-controlled case series analysis) from the Quebec study, involving GSK’s other AS03-adjuvanted H1N1 pandemic vaccine Arepanrix, was submitted in December 2012 (refer to FUM 100.3 adopted March 2013).

In support of the application, the MAH submitted details of their proposals for additional epidemiological analysis in the Quebec study, to mitigate potential biases and allow adjustment for potential confounders (such as medically attended respiratory infections). The MAH has also submitted...
details of their non-clinical research proposals to investigate the relationship between Pandemrix and narcolepsy.

The proposed change to the product information concerns the description of the above obligations in Annex II (post authorisation measures). A summary of the analyses and investigations the MAH is planning to undertake, with timelines until December 2014 were provided.

The MAH has explained the rationale for the proposed submission dates for the various aspects of the narcolepsy investigation program; conservative timelines have been proposed as some of the studies are dependent on results of previous investigations and experiments which are not yet complete. The MAH also plans to group related findings and results into the same submissions to the EMA/CHMP, which the MAH considers will facilitate understanding and interpretation on the data. The MAH has indicated that significant or unexpected results would be communicated to EMA/CHMP without delay. This is accepted.

In response to the request to reflect the outcome of the Article 5(3) referral procedure as an RMP commitment, the MAH has now included in the RMP (as a Pharmacovigilance activity in relation to the identified risk of narcolepsy and the MAH’s research program to investigate the root cause of the association with Pandemrix) a summary of their proposed plan to evaluate the potential for immunological differences between Pandemrix and Arepanrix.

In relation to the commitment to investigate the immunological differences between Pandemrix and Arepanrix with a view to finding an explanation for the risk of narcolepsy, the MAH has now provided further detail on the quality composition and manufacturing processes of Pandemrix and Arepanrix, and highlighted the main differences. The MAH have also revised their investigation plan on this aspect, previously proposing to analyse B cell receptor repertoires in mice immunised with either vaccine. The MAH now proposes to analyse antibody responses in sera samples from paediatric clinical studies in which Pandemrix and Arepanrix were directly compared. This alternative approach has potential to identify any differences in immunological response to the two vaccines in terms of the strength of the response and any subsequent differences in the H1N1 epitopes targeted. It is anticipated to report results by the end of 2014, a year earlier than the original plan. It is acknowledged that this analysis will not be able to link any observed differences to narcolepsy but needs to be seen in the context of the wider studies the MAH are conducting into the root cause of narcolepsy. This updated plan has been reflected in the RMP.

Taking into consideration the MAH’s plans for their research agenda on narcolepsy and their reflection in Annex II, the CHMP considers that these changes do not have an impact on the benefit/risk balance.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

<table>
<thead>
<tr>
<th>Variation requested</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.I.z</td>
<td>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</td>
</tr>
</tbody>
</table>

To update the obligations related to narcolepsy currently included in Annex II of the Pandemrix MA by
listing the proposed non-clinical and epidemiological studies planned to further elucidate the role of Pandemrix in the onset of narcolepsy.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

**Conditions and requirements of the marketing authorisation**

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

**Conditions or restrictions with regard to the safe and effective use of the medicinal product**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can submit at the same time.

- **Additional risk minimisation measures**

The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 vaccine administered to each patient, in order to minimise medication errors and aid patients and health care professionals to report adverse reactions. This may include the provision by the MAH of stickers with invented name and batch number with each pack of the vaccine.

The MAH shall agree with Member States on mechanisms allowing patients and health care professionals to have continuous access to updated information regarding Pandemrix.
The MAH shall agree with Member States on the provision of a targeted communication to healthcare professionals which should address the following:

- The correct way to prepare the vaccine prior to administration.
- Adverse events to be prioritised for reporting, i.e. fatal and life-threatening adverse reactions, unexpected severe adverse reactions, adverse events of special interest (AESI).
- The minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and the identification of the vaccine administered to each subject, including the invented name, the vaccine manufacturer and the batch number.
- If a specific notification system has been put in place, how to report adverse reactions.

**Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduct a retrospective epidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects:</td>
<td></td>
</tr>
<tr>
<td>- Test-negative case-control study results</td>
<td>December 2013</td>
</tr>
<tr>
<td>- Re-analysis of the dataset with adjustment for medically-attended respiratory infection/influenza-like illness</td>
<td>December 2013</td>
</tr>
<tr>
<td>- Re-analysis of the dataset after exclusion of symptomatic controls after 1 year follow-up (if applicable); and description of the clinical follow-up of cases for 2 years.</td>
<td>December 2014</td>
</tr>
<tr>
<td>Conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy:</td>
<td></td>
</tr>
<tr>
<td>- If deep sequencing approach is proven feasible:</td>
<td></td>
</tr>
<tr>
<td>- identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccinees</td>
<td>June 2014</td>
</tr>
<tr>
<td>- if identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients</td>
<td>December 2014</td>
</tr>
<tr>
<td>- Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*-0602 binders and with additional proteins using T2 cells as antigen-presenting cells</td>
<td>December 2014</td>
</tr>
<tr>
<td>- Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage.</td>
<td>June 2014</td>
</tr>
<tr>
<td>- Evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared.</td>
<td>December 2014</td>
</tr>
</tbody>
</table>