## COMMISSION ON HUMAN MEDICINES (CHM) COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on Friday 18th November 2022 at 11:30 via videoconference

### **Participants Present**

#### **Members**

Professor Sir M Pirmohamed (Chair)

Professor G Dougan<sup>1</sup>

Mr VI G Fenton-May

Professor N French

Professor D Goldblatt1

Ms S Hunneyball

Professor K Hyrich

Professor H J Lachmann

Mr R Lowe1

Dr S Misbah

Professor Y Perrie

Professor S Price

Professor C Robertson<sup>2</sup>

Professor K M G Taylor

Dr R Thorpe

Professor M Turner

Professor S Walsh

Mrs M Wang

Professor C Weir

## **Apologies**

Professor J Breuer Professor P J Lehner

Dr A Riordan

## **Observers**



Professor W S Lim



### **Secretariat**

Ms P Edwards Mr F Islam

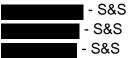
## **Professional Staff of MHRA Present**

#### **Principal Assessors**

Dr J Bonnerjea - HQA



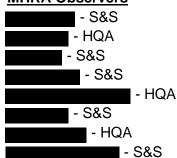
### Presenters supporting specific items



- MHRA-NIBSC - HQA

- HQA

### **MHRA Observers**





19th January 2023

### <u>Key</u>

**HQA** = Health Quality & Access Group **S&S** = Safety & Surveillance Group

NIBSC = National Institute for Biological Standards & Control

<sup>&</sup>lt;sup>1</sup> left during item 4

<sup>&</sup>lt;sup>2</sup> left during item 3

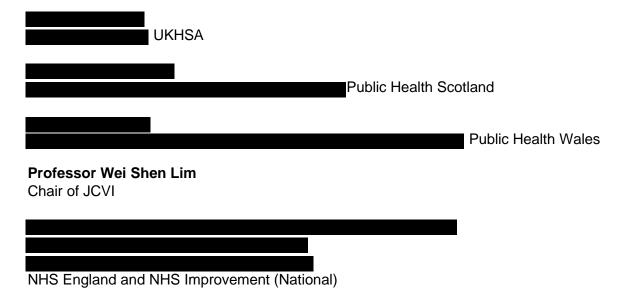
#### 1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

## 1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

- 1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex** II to the minutes.
- **1.4** Apologies were received from Professors Breuer, Lehner and Dr Riordan for this meeting.
- **1.5** The Chair welcomed the following observers to the meeting:



- 2. Vaxzevria & addition of tinnitus to the product information following EU review PLGB 17901/0355 0072
- The EWG considered an assessment of tinnitus following COVID-19 vaccination, which included an EU review by the PRAC of Vaxzevria and tinnitus, UK Yellow Card data and Pfizer and Moderna's assessments of tinnitus. The EU review proposed to add tinnitus as an undesirable effect for Vaxzevria.
- 2.2 The EWG discussed that the evidence for an association between Vaxzevria and tinnitus was not particularly strong, however the clinical trial imbalance does provide some

evidence. The EWG agreed that the evidence concerning the mRNA vaccines does not suggest a signal. The EWG also noted that Janssen has a signal for tinnitus which has been added to the SmPC.

- 2.3 Regarding a potential mechanism of action, the EWG discussed whether this could be secondary to neurological events in some cases. The EWG also discussed how a study on the mouse phenotype suggested a correlation between infection immunity and hearing, which was linked to development of hair cells and mucosal epithelia, and therefore the virus could be targeting similar receptors. A link with pneumonia and tinnitus has also been suggested and the EWG noted that tinnitus may be secondary to inflammatory conditions but overall, no mechanism has been identified.
- The EWG also discussed how the onset time of the events could be suggestive of reactogenicity and the duration of events was typically short. The EWG also noted that the background prevalence of tinnitus is also high.
- The EWG queried Pfizer's exclusion of a large number of spontaneous reports due to low quality during their tinnitus assessment and what the result was when these reports were included. The MHRA stated that they will contact the MAH about exclusion of spontaneous reports and the impact on the analysis.
- 2.6 The EWG discussed the proposed PIL wording of 'persistent' ringing in the ears which may be alarming to patients and also does not reflect the spontaneous data which showed a short reaction duration. The EU SPC section 4.8 wording notes 'tinnitus' but not persistent.
- 2.7 The EWG was in agreement to update the Vaxzevria product information to include tinnitus as an undesirable effect but that it is possible the GB PIL wording should be amended to 'tinnitus' and not 'persistent ringing in the ears'.
- 3. mRNA vaccines & addition of heavy menstrual bleeding to the product information
- 3.1 The EWG was informed that the European Union (EU) Pharmacovigilance Risk Assessment Committee (PRAC) had recommended that heavy menstrual bleeding should be added to the product information for Pfizer and Moderna COVID-19 vaccines as an undesirable effect of unknown frequency. This was based on the PRAC conclusion following their most recent review of this issue that there is at least a reasonable possibility that the occurrence of heavy menstrual bleeding is causally associated with these vaccines.
- The EWG was presented with an updated review of heavy menstrual bleeding with the Pfizer and Moderna COVID-19 vaccines. This included updated UK usage and Yellow Card data (data lock point 26<sup>th</sup> October 2022) as well as data in the final PRAC assessment reports for the issue of heavy menstrual bleeding with Pfizer and Moderna COVID-19 vaccines that had not previously been considered by the EWG, namely new published literature, company observed vs expected analyses and updated reviews of clinical trial data and serious reports of heavy menstrual bleeding.
- The EWG considered the available evidence on the risk of heavy menstrual bleeding with Pfizer and Moderna COVID-19 vaccines based on the information presented at the meeting. The EWG discussed the high background prevalence of heavy menstrual bleeding and that many women experience sporadic changes in the degree of menstrual bleeding generally. The EWG considered that the new data presented did not provide conclusive evidence to support a causal link between changes to heavy menstrual bleeding and Pfizer and Moderna COVID-19 vaccines.

- The EWG discussed the update to EU product information regarding heavy menstrual bleeding and whether the GB product information should be updated in line with the PRAC agreed wording. The EWG considered that given public concerns as to whether there is a potential impact on fertility following reports of menstrual disorders after vaccination against COVID-19, any wording about heavy menstrual bleeding as a possible side-effect needed careful consideration to avoid unnecessary alarm to vaccine recipients. The EWG also acknowledged that there may be public concern if GB product information was not aligned with the EU regarding heavy menstrual bleeding despite the lack of evidence for a causal association with mRNA vaccines.
- 3.5 The EWG noted the PRAC agreed wording for Pfizer and Moderna COVID-19 vaccines product information included a descriptive statement that most cases appeared to be non-serious and temporary in nature. The EWG suggested that if heavy menstrual bleeding were to be added to GB product information, the MHRA should consider whether it would be possible to also include a statement in the patient leaflet that there is no evidence of any negative impact of COVID-19 vaccines on fertility. The EWG also suggested that the MHRA should consider whether there was a need for an updated review of heavy menstrual bleeding and AstraZeneca COVID-19 vaccine.
- The EWG agreed that the benefit risk balance for both the Pfizer and Moderna COVID-19 vaccines remained positive.
- 3.7 The EWG were informed about an editorial<sup>1</sup> by Victoria Male on COVID-19 and menstruation published on 17<sup>th</sup> November 2022.
- 3.8 The EWG were asked to provide any additional comments on heavy menstrual bleeding and mRNA COVID-19 vaccines ahead at the planned consideration of this issue at the CHM meeting of 24<sup>th</sup> and 25<sup>th</sup> November 2022 once members had been able to consider the MHRA written assessment report on this issue.
- 4. Comirnaty 3 micrograms/dose concentrate for dispersion for injection (tozinameran) PLGB 53632/0008 (EC reliance)
- 4.1 The EWG heard that a line extension application for Comirnaty 3 micrograms/dose concentrate for dispersion for injection has been submitted via the EC Decision Reliance procedure.

  It is proposed for use as a 3-dose primary series in infants and children aged 6 months to 4 years. The EWG noted that Comirnaty (original) is already approved as a 2 dose primary series and as a booster dose in individuals aged ≥ 5 years (
- 4.2 The EWG heard an overview of the quality aspect of the application. The similarities and differences between the three authorised Comirnaty prototype products and the proposed paediatric (6 months to 4 years) were discussed.
- It was emphasised that there are no changes made to the drug substance (DS) or drug product (DP) manufacturing processes. The formulation is identical for the RNA/dose-presentations, only the fill volume or the requirement for dilution prior to administration are different.

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<sup>&</sup>lt;sup>1</sup> https://pubmed.ncbi.nlm.nih.gov/36395209/

- Once diluted, 10 doses can be delivered for the 3 µg dose-presentation with the use of low dead-space syringes and needles.

  It is acknowledged that physical and chemical stability, as well as microbiological studies of the undiluted and diluted finished product are satisfactory.
- 4.5 Feedback to the EWG was given regarding the information currently specified in the SmPC with respect to the 12 hours in-use shelf-life (post-punctured shelf-life) following a comment made at the CHM on 27th October for Comirnaty Original/Omicron BA.4/5 product. It was acknowledged that only when microbiological contamination could be ruled out should one consider storing the vial for longer, particularly when the environments of the diluted product could be different in various settings.
- Whilst the information presented in the Green Book regarding the in-use shelf-life is the same as that specified in the SmPC, i.e. 12 hours in-use shelf-life, reassurance was provided to the Committee that the Specialist Pharmacy Service (SPS) already recommends the product is to be used immediately. Therefore, it was agreed that to avoid confusion and inconsistency between the different literature sources, no change to the "12 hours" wording in the Green Book is warranted.
- **4.7** There are no major quality issues precluding the approval of this application.
- The EWG heard a summary of the clinical data from the pivotal study C4591007 in infants and children aged 6 months to < 5 years. The EWG noted that preliminary immunogenicity results with a 2 dose (3 micrograms) primary series had shown inferior immunogenicity results in the 2–4-year-old stratum compared with young adults aged 16-25 years of age. In view of this, in agreement with the European Medicines Agency, the study was amended to a 3 dose (3 microgram) primary series.
- 4.9 The EWG heard that the prespecified immunobridging criteria were met in both age strata following a 3 dose primary series. Supportive clinical efficacy data post dose 3 demonstrated 73% efficacy at preventing symptomatic COVID-19 at a time when Omicron variants were the dominant circulating strains. The EWG noted that efficacy appeared to be better following the 3rd dose compared with post dose 2. The EWG highlighted that in view of the need for a 3 dose primary series infants and children aged 6 months, it will be important to review what proportion of individuals in this age group receive all 3 doses and effectiveness data in post authorisation effectiveness studies.
- The reactogenicity profile in 2–4-year-olds was similar to that seen in older children. In infants and young children < 2 years age-appropriate reactogenicity events were reported in the study and the EWG noted that, reflective of this, 3 new adverse events have been included in the product information: 'Irritability', 'drowsiness' and 'injection site tenderness'. The majority of reactogenicity events were mild to moderate in intensity and resolved within two days. No new safety concerns were identified. The EWG considered that, in-line with the current advice for 5–11-year-olds, the 15-minute observation period could be temporarily suspended since the risk of anaphylaxis was not expected to be higher in this age group (children are less prone to anaphylaxis) and they will be monitored by parents.
- 4.11 The EWG noted some inconsistencies in the patient information leaflet whereby instead of referring to 'your child' it sometimes reverts back to 'you'. This will be taken forward with the company and will need to be addressed in the GB and EU leaflet.
- 4.12 The updated Risk Management Plan (RMP) was summarized for the EWG. The EWG was informed that the company proposed no changes to the 'safety specification' or 'risk

minimisation plan' sections of the RMP. The 'pharmacovigilance plan' had been updated to include children aged 6 months to 4 years of age in the populations being investigated in five post-authorisation studies.

- The EWG was also informed of post-authorisation safety data published by the Centers for Disease Control and Prevention (CDC) in the United States, which reported a high incidence of vaccination errors in patients aged 6 months to 5 years of age who received an mRNA vaccine. This was supplemented by data from an ad hoc analysis of vaccination errors provided by the company at the request of the MHRA, which also found a high incidence of vaccination errors in the US.
- The EWG endorsed the two post-authorisation commitments proposed by the MHRA, requiring that the company submit a 3-month Summary Safety Report on use in the proposed new population of children and also make proposals for studying vaccine effectiveness in this group. In addition, the EWG requested that the MHRA present the available data on vaccination errors with the COVID-19 vaccines to stakeholders in national bodies involved in vaccine deployment and administration. The EWG asked for written comments on the presentation to be requested from paediatric experts.

The EWG agreed with the post-marketing approval measures requested by the EMA and MHRA and that this line extension application is approvable.

- 5. Minutes of the COVID-19 VBR EWG meetings (Drafts)
  - 01. Friday 04 June 2021
  - 02. Friday 17 September 2021
  - 03. Friday 24 September 2021
  - 04. Friday 12 August 2022
  - **05. Thursday 25 August 2022**
  - 06. Tuesday 20 September 2022

Queries were raised to the minutes of 12<sup>th</sup> August and 20<sup>th</sup> September, which have been reviewed, resolved and endorsed by the Chair. All the above listed minutes have been endorsed as a true and accurate record of the meetings.

#### 6. Any Other Business

6.1 of the National Institute for Biological Standards and Control (NIBSC) gave an update to the EWG on the issue with two batches of the Pfizer presentation for 5-11 year olds.

## 7. <u>Date and time of next meeting</u>

The next meeting has been scheduled for Friday 2<sup>nd</sup> December 2022 at 11:30.

The Meeting today started at 11:34 and ended at 13:53.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

### Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

#### **Chair and Members**

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

#### **Invited experts**

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

### **Observers**

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

**Annex II** 

The following participants declared interests and other relevant interests at the meeting today:

**Professor Sir Munir Pirmohamed** - <u>NPNS</u> AstraZeneca - Research grant to UOL to support PhD in drug interactions.

Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3<sup>rd</sup> November 2020.

AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).

Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

**Professor French** - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

**Ms Hunneyball** - Other relevant interest — writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

**Professor Hyrich** – <u>NPNS</u> - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. <u>NPNS</u> Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. <u>NPNS</u> in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

**Professor Lachmann – Other relevant interest** as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

**Dr Misbah** - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

**Professor Perrie** - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

**Professor Price** - NPNS in GSK and AstraZeneca — which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

**Mrs Wang** - Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

**Professor Weir** - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

### **Observers**

