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

Minutes of the meeting held on Friday 29th April 2022 at 11:30 via videoconference

#### **Participants Present**

#### **Members**

Professor Sir M Pirmohamed (Chair)

Professor J Breuer

Mr VI G Fenton-May

Ms S Hunneyball

Professor H J Lachmann

Professor P J Lehner<sup>1</sup>

Mr R Lowe

Professor Y Perrie

Professor S Price

Dr A Riordan

Professor C Robertson<sup>1</sup>

Professor K M G Taylor

Dr R Thorpe

Professor M Turner

Professor S Walsh

Mrs M Wang

Professor C Weir

#### **Apologies**

Professor G Dougan

Professor N French

Professor D Goldblatt

Professor K Hvrich

Sir M Jacobs

Dr S Misbah

Professor T Solomon

#### Observers<sup>2</sup>



#### **Secretariat**



#### <u>Lawyer</u>

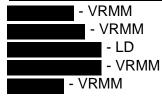
#### **Professional Staff of MHRA Present**

#### **Principal Assessors**

Dr J Bonnerjea - LD

- VRMM

#### Presenters supporting specific items



#### **MHRA Observers**

- VRMM
Dr S Branch - VRMM
- VRMM
- VRMM
- MHRA-Policy
- LD
- VRMM

Mr P Tregunno - VRMM



#### Key

**LD** = Licensing Division

**VRMM** = Vigilance & Risk Management of Medicines

<sup>&</sup>lt;sup>1</sup> joined during item 5

<sup>&</sup>lt;sup>2</sup> left after item 4

<sup>&</sup>lt;sup>3</sup> joined during item 3

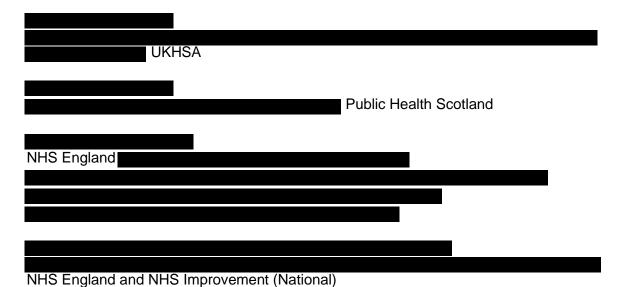
#### 1. Introduction and Announcement

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 Dougan French, Goldblatt, Hyrich, Solomon, Dr Misbah, and Sir Michael Jacobs for this meeting.
- **1.5** The Chair welcomed the following observers to the meeting:



#### 2. Proposed updates to AZ COVID-19 vaccine section 4.6 and 5.3

The EWG was presented with updated safety and efficacy information relating to AZ COVID-19 exposure in pregnant and breastfeeding women. The data were requested and assessed by the European Medicines Agency's (EMA's) Pharmacovigilance and Risk Assessment Committee (PRAC) and shared with MHRA.

- 2.2 The EWG heard that there were no new pre-clinical or clinical data available in these patient populations. Post-marketing data and a review of the available literature did not raise a new safety concern.
- 2.3 The MHRA concurred with the PRAC conclusion that no updates to sections 4.6 and 5.3 were warranted based on the new data and that the current information adequately reflected the available evidence.
- 2.4 The MHRA proposed to fully align the GB PI with the EU PI. The EWG supported this proposal, however, it recommended to retain a current signposting present in section 4.6 of the GB PI.

#### 3. Autoimmune hepatitis and mRNA COVID-19 Vaccines

- The EWG were presented with a review of autoimmune hepatitis with the Moderna and Pfizer/BioNTech COVID-19 vaccines. The EWG were informed that the signal assessment was initiated by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee, who concluded that there was no association between autoimmune hepatitis and the mRNA COVID-19 vaccines.
- The EWG were informed that there had been a small number of Yellow Card reports of autoimmune hepatitis, with reporting rates of 0.02 and 0.03 per 100,000 doses for the Pfizer/BioNTech and Moderna vaccine respectively. The EWG noted one literature report for the Moderna vaccine that included a positive rechallenge following the second dose. The EWG were presented with the company's review which found only a small number of reports of autoimmune hepatitis and an observed vs expected analysis finding the number of reports to be well below the expected number of reports.
- 3.3 The EWG were informed of the UK Health Security Agency (UKHSA) investigation into cases of hepatitis in children with an adenovirus currently considered as the cause of the hepatitis events. The EWG noted that there was no link to the COVID-19 vaccines as none of the cases having received a COVID-19 vaccine.
- The EWG concluded that the available evidence does not support a causal association between the Moderna or Pfizer/BioNTech vaccines and autoimmune hepatitis.

#### 4. Updated overview of fatal events reported following COVID-19 vaccination

- 4.1 The EWG was presented with an updated trends analysis of Yellow Card reports received by the MHRA that cite a fatal outcome in association with COVID-19 vaccination. The updated analysis also sought to identify whether there are any possible new signals of concern that have not been identified previously within these fatal reports.
- The EWG noted the summary of previous reviews presented to the EWG of reports with a fatal outcome following COVID-19 vaccination (January 2021, February 2021 and March 2022). These reviews reassured the EWG that COVID-19 vaccination was not causally related to the reports with a fatal outcome reviewed on those occasions.
- 4.3 The EWG was presented with all relevant data from available sources including UK vaccine usage data, UK reports with a fatal outcome received in association with a COVID-19 vaccine, MHRA observed versus expected analysis for all-cause mortality and data published by other regulators.

- 4.4 The EWG was informed of the extensive coverage of the UK COVID-19 vaccination programme to date which has administered over 140 million vaccinations in the UK with over 90% of the population aged 12 years and over receiving at least one dose of COVID-19 vaccine.
- The EWG noted that reports with a fatal outcome received to date remain concentrated in older age groups which is expected given that this population often have multiple comorbidities and increased frailty with old age. Fatal reports have also been received in younger age groups including 5 fatal reports in those aged under 18 years old. Review of these paediatric reports did not identify any paediatric specific safety issues with the COVID-19 vaccines as most reports had confounding factors for the fatal outcome. A qualitative review of UK reports has not identified a novel pattern of concern with respect to the specific fatal term reactions underpinning the reported cases outlined in the assessment presented to the EWG.
- The EWG noted that the observed vs expected analyses for all-cause mortality do not suggest any excess reporting of fatal events within 7 days of receiving any of the three vaccines either overall or following the first dose. The EWG agreed that the observed vs expected analyses are generally reassuring although uncertainties in the true underlying mortality risk, given that those at the greatest and smallest risk may be less likely to be vaccinated and hence the population-level mortality risk estimates used to calculate the expected may not be representative of the actual risk in the vaccinated population, limits this approach.
- The EWG noted that public information provided by other regulatory bodies has not identified any new concerns over the received reports with a fatal outcome. There is some variability in the level of detail other regulators provide with respect to these reports. Some summaries provide no figures for fatal cases whilst others offer a short breakdown of the specific reactions involved and whether a causal relationship was suspected.
- The EWG commented that the data informing this update appeared comprehensive and provided reassurance given that the number of different approaches utilised did not identify a new signal of concern. The EWG commented that as the UK vaccination programme continues to progress with use in younger age groups and boosters for clinically vulnerable/elderly patients there is a need to remain vigilant for reports with a fatal outcome and continue this type of review.
- 4.9 The EWG commended the MHRA for the communications and public summaries provided to date and emphasised the continued need for transparency in order to further foster public trust in the information provided.
- **4.10** The EWG then considered the following 3 questions:

Question 1: Based on the evidence presented does the EWG agree that no regulatory action is required?

The EWG agreed that no regulatory action is required at present.

Question 2: Does the EWG agree that the benefit risk remains positive for each of the following vaccines?

- Pfizer/BioNTech
- Moderna
- AstraZeneca

The EWG agreed that the benefit risk remains positive for all these COVID-19 vaccines.

Question 3: Does the EWG have any suggestions or amendments to the current wording of the events with a fatal outcome subsection in the MHRA Coronavirus vaccine weekly summary of Yellow Card reporting publication?

The EWG recommended that the entry could be updated to provide figures outlining the context in which reports with a fatal outcome are being received. It would be important to communicate how many deaths occur in the UK for a set period of time (e.g. day or week) as well as the impact of the UK COVID-19 vaccine programme in saving lives and preventing hospitalisation.

The EWG also noted, where deaths have been linked to specific adverse reactions e.g. thrombosis with thrombocytopenia syndrome, then the summary should reference the measures that were taken to mitigate these risks.

#### 5. Vaxzevria Clinical AR - Booster Indication

A type II variation (GB) application has been submitted by the MAH to update the product information regarding the use of Vaxzevria as a heterologous booster "after another authorised vaccine". While the benefit/risk balance is considered positive for a homologous booster, it is considered negative for a heterologous booster, especially after an mRNA vaccine: immunogenicity data available do not show non-inferiority of antibody levels to those achieved after a homologous booster of an mRNA vaccine and the potential risk of thrombosis with thrombocytopenia syndrome (TTS) following the first exposure to AZD1222 cannot be estimated on the basis of the data provided. Therefore, a major objection has been raised, which has been endorsed by the EWG.

#### 6. Any Other Business

None.

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

The next meeting has been scheduled for Friday 6th May 2022 at 14:30.

The Meeting today started at 11:31 and ended at 12:48.

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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 Breuer** NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

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

**Professor Lehner** - Other relevant interest — Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

**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).

**Dr Riordan** - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial -received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases). Member of the independent Data Safety Monitoring Board for COV-BOOST trial.

**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** - <u>NPNS</u> - Imperial College and <u>Other relevant interest</u> arising from his department collaborates with Imperial College on a number of clinical trials.

#### **Observer**

