NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

Minutes of the Ad Hoc Videoconference Meeting held on Tuesday 6th April 2021 at 15:00 via MS Teams.

Commissioners Participated

Professor Sir M Pirmohamed (Chair)

[redacted]

Apologies

[redacted]

Invited Experts

[redacted]

Observers

[redacted]

Secretariat

[redacted]

[1] joined at 15:30

[2] joined at 15:50

[3] left at 16:00

Professional Staff of MHRA Participated

VRMM led meeting

Dr S Branch – VRMM

VRMM Presenter

[redacted]

Internal Observers

[redacted]

Ms R Arrundale - MHRA-Policy

[redacted]

Mr S Hallworth - Comms

[redacted]

Dr J Raine - MHRA CEO

Dr C Schneider - MHRA-NIBSC

[redacted]

[redacted]

01 July 2021

Key

LD = Licensing Division

VRMM = Vigilance & Risk Management of Medicines

NIBSC = National Institute for Biological Standards & Control

MHRA CEO = Chief Executive

1. Apologies and Announcements

1.1 The Chair reminded Commissioners, 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 The Chair reminded Commissioners, Invited Experts and Observers to declare their non-personal specific, non-personal non-specific and other relevant interests in the agenda items.

Commissioners were reminded that they are not permitted to hold any personal interests in the pharmaceutical industry, in line with the Code of Practice.

Participants declared interests and other relevant interests for this meeting listed at **Annex I** to the minutes.

1.3 The Chair welcomed the following invited experts who participated for this meeting:

[redacted] MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London

[redacted] UCL School of Pharmacy, London

[redacted] ember of the Clinical Trials, Biologicals & Vaccines Expert Advisory Group (CTBVEAG)

[redacted] RGN, RCN Nurse Practitioner, PGCEA, PG Cert NMP, Queens Nurse Advanced Nurse Practitioner

1.4 The Chair also welcomed the following observers for this meeting:

[redacted] JCVI Scientific Secretariat, Secretary to the Joint Committee on Vaccination and Immunisation, Public Health England

[redacted]
JCVI

[redacted]
Deputy Chief Medical Officer

1.5 Apologies were received from [redacted] due to the short notice of arranging this meeting.

2. **Paper**

Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

Background on previous activities

This extraordinary meeting of the CHM was called following the last CHM on 4 April 21 in light of new data becoming available and including new regulatory proposals from the company. The CHM was to be informed of factors related to the use of the vaccine outside of the remit of the CHM which are influencing the previous proposal for an age restriction on use of the AstraZeneca vaccine. The Commission was asked for advice on the benefit risk balance in light of the most recent data and for comments on proposed updates to the Regulation 174 product information.

2.1 The Commission was presented with slides provided by AstraZeneca which the company had presented to the VBR EWG earlier on 6th April. The slides summarised global data on reports of thromboses with concurrent thrombocytopenia, provided observed vs. expected analyses for the events and summarised the benefits of AstraZeneca vaccination. The data lock point for AstraZeneca's presentation was 31st March. The Commission noted that to estimate the background rate of these events, the company performed an analysis using events reported in a large US health insurance claims database, within the period of 1 January 2019 to 31 December 2019.

2.2 The Commission commented that the company's approach of using a cumulative mortality rate was likely to overstate the benefits of the vaccine. The Commission remarked that the company had focussed on cerebral venous sinus thrombosis (CVST) events but that there were likely to be other sites affected by the same mechanism.

2.3 The Commission also commented on the use of a US insurance database to perform the observed vs expected analysis and noted that this data source may not be comparable to the UK population and that the data was likely skewed. The Commission also commented that the database was likely to be poorly representative of older people, most of whom use Medicare. The MHRA noted that the company proposed to perform a similar study using UK databases but that this was still in the planning phase.

2.4 The Commission was informed that AstraZeneca would be performing mechanistic studies, which were currently being planned and would be included in the Risk Management Plan.

2.5 The Commission heard an update on the latest data held by MHRA up to the data lock point of 31 March 2021. It was reported that the majority of cases related to CVST alongside thrombocytopenia, but other thromboembolic events had also been reported, and that a higher proportion of CVST cases were fatal compared to other sites affected by thrombosis. The meeting heard that the quality of cases had greatly improved since the introduction of the proforma.

2.6 Incidence rates of the events by age group were also presented to the meeting, alongside epidemiological data on the vaccines impact on reducing COVID-19 cases, long COVID, hospitalisations, ICU admissions and deaths. The Commission commented that the fatality rate presented by the company was around 25%, which is in line with the UK data presented by the MHRA.

2.7 The Commission noted the value of consistency in product information from international regulators in the context of a global pandemic. The Commission was informed of discussions taking place in other regions.

2.8 Having considered the further data available, Commission advised that the benefit-risk remained positive overall and that in light of the data presented to the Commission, an age cut-off for use of the AstraZeneca vaccine was no longer advised. The Commission commented that it was important that the public were made aware of the information available at present and that the decisions made based on the benefits and risks could change as more data become available. The Commission reviewed the proposals for updates to the Regulation 174 product information which had been drafted based on previous CHM advice. The proposals for the Information for healthcare professionals (HCPs) included a contraindication in section 4.3 in patients with a history of major venous and arterial thrombosis with thrombocytopenia and in patients who experienced these events after vaccination. The Commission agreed with the proposed 4.3 wording. In section 4.4 a warning was proposed to describe what is currently known about the risk, signs and symptoms for healthcare professionals to be aware of and advice for healthcare professionals to refer patients to haematologists for treatment. The Commission discussed whether the proposed statement that causality with the vaccine had not been established was necessary and agreed to include this statement. The Commission suggested that information for HCPs should mention that patients should be referred to a secondary care facility with haematology expertise promptly.

2.9 Following discussion, the Commission advised that the existing statement on pregnancy should remain, with reference to the 4.4 and 4.8 warnings on the risk thromboembolism with thrombocytopenia. The Commission agreed with a warning in section 4.8 although it was advised that the risk was still considered extremely rare.

Summary of CHM advice
CHM advised that:

- *The data presented did not support an age restriction for use of the AstraZeneca vaccine.*
- *The current understanding of the risks should be communicated*
- *The Commission advised on the key messages for updates to the Regulation 174 product information.*

3. Any Other Business

3.1 None.

4. Date and Time of Next Meeting

The next scheduled meeting is to be held on Thursday 8th April 2021 at 10:00 & Friday 9th April 2021 at 09:30.

Annex I

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

Professor Sir Munir Pirmohamed - NPNS 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 3rd 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).

[redacted] - NPNS - GlaxoSmithKline, Sanofi, Pfizer

[redacted] NPNS – Janssen, Pfizer & GlaxoSmithKline.
Other relevant interest - Other members of the department at UCL are collaborators on trials of the Oxford, Novavax and Imperial College London COVID vaccines. [redacted] is not responsible for the department and is not directly involved in the trials.

[redacted] - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which [redacted]

[redacted] - NPNS - Sanofi, Pfizer, Janssen

[redacted] - NPNS - Janssen, GlaxoSmithKline, Pfizer, AstraZeneca, Sanofi. The Unit in which [redacted] works at University College London is coordinating the Imperial Covid Vaccine trials, however [redacted] is not involved.

[redacted] - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

[redacted] - 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 [redacted]

[redacted] – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on [redacted] medical records.
The family of [redacted] lives with several rare diseases and conditions, some of which result in epileptic fits.

[redacted] - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded [redacted] post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.