OFFICIAL – SENSITIVE COMMERCIAL CHM/COVID19VBREWG/2021/24th MEETING

NOT FOR PUBLICATION

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

Minutes of the meeting held on Friday 14th May 2021 at 14:00 via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)

Professor J Breuer

Professor G Dougan

Mr VI G Fenton-May

Professor N French

Professor D Goldblatt

Ms S Hunneyball

Professor K Hyrich

Sir M Jacobs

Professor P J Lehner

Mr R Lowe

Dr S Misbah

Professor Y Perrie

Professor S Price¹

Dr A Riordan²

Professor T Solomon

Professor K M G Taylor

Dr R Thorpe

Professor M Turner³

Dr S Walsh

Mrs M Wang

Apologies

Professor H J Lachmann Professor C Robertson

Professor C Weir

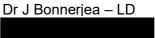
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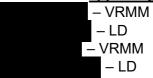
¹ joined during item 2

<u>Professional Staff of MHRA Present</u> <u>Principal Assessors</u>

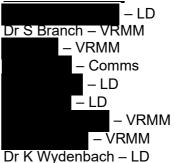
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Presenters supporting specific items



MHRA Observers





16th February 2023

<u>Key</u>

LD = Licensing Division

VRMM = Vigilance & Risk Management of Medicines

Comms = MHRA Communications

² joined during item 4

³ left during item 5

1. Introduction and Announcements

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 Lachmann, Robertson and Weir for this meeting.

2. Review of the possible risk of neurological autoimmune conditions with COVID-19 vaccines

- The EWG was presented with an assessment of data for the adverse events of multiple sclerosis, optic neuritis, transverse myelitis and Neuromyelitis Optica Spectrum Disorder (NMOSD) reported following vaccination with the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 Vaccines. The assessment included a review of the UK Yellow Card data, data from the most recent safety summary surveillance report for each of the vaccines, and epidemiological analyses (observed vs expected analyses of Yellow Card reports and rapid cycle analyses using the CPRD).
- 2.2 For the AstraZeneca vaccine, the EWG were informed that the number of reports of neurological autoimmune conditions was low in the context of the usage of the AstraZeneca vaccine. For transverse myelitis, the majority of reports met the case definition, but had very rapid onset times not associated with transverse myelitis. For multiple sclerosis and optic neuritis, the majority of reports were consistent with reactogenicity reactions and were transient, short-duration reactions. Company observed vs expected analysis did not identify an increase in these events.
- 2.3 For the Pfizer/BioNTech vaccine, the EWG were informed that there had been limited reports of multiple sclerosis, optic neuritis or transverse myelitis and no reports of NMOSD. The EWG noted that there was no clear patterns of onset times or occurrence after a specific dose, and company data did not show an increased risk of these events. For all events the number of reports was small in the context of the use of the vaccine.
- 2.4 For the Moderna vaccine, the EWG noted there had been no Yellow Card reports of multiple sclerosis, optic neuritis, transverse myelitis or NMOSD and that there were very few reports from international data.

- The EWG were presented the MHRA epidemiological data, with observed vs expected analysis identifying a signal of transverse myelitis for the AstraZeneca vaccine assuming 100% reporting for all age groups, and for the Pfizer/BioNTech vaccine assuming 50% reporting in the under 50 years age group, and 25% reporting in the 50-64 years age group. Rapid cycle analysis did not identify any signals for any of the neurological autoimmune conditions or vaccines.
- The EWG considered that the majority of reports of multiple sclerosis, optic neuritis and NMOSD were not related to new onset of these events, with the reports describing either flare-up of these events or reactogenicity events. For transverse myelitis, the EWG considered that for the AstraZeneca vaccine, while reports did meet the case definition, the reports did not relate to new-onset of transverse myelitis. The EWG considered that transverse myelitis should continue to be closely monitored and was aware of potential epidemiological studies that would be investigating this. The EWG concluded that the available evidence did not support any updates to the product information for any of the COVID-19 vaccines.

3. Risk of Capillary Leak Syndrome with COVID-19 Vaccine AstraZeneca

- The VBR EWG was reminded that it had previously considered an assessment of UK cases of capillary leak syndrome (CLS) reported following vaccination with COVID-19 Vaccine AstraZeneca at its meeting on 12 April 2021. At that time the EWG advised that a causal association could not be determined based on the data available, and that the signal should be closely monitored.
- The EWG was presented with an updated review of this signal which included an assessment of UK cases of CLS reported for COVID-19 Vaccine AstraZeneca via the Yellow Card Scheme, together with an assessment of a cumulative review of worldwide clinical study and post-authorisation cases and a literature review submitted by the company.
- The EWG agreed that the currently available data did not suggest an association between COVID-19 Vaccine AstraZeneca and CLS. Causality assessment was difficult in some cases because the patients had a prior history of CLS or other significant illness. Causality was also considered unlikely in some cases due to the time to onset being inconsistent with a vaccine-related effect. The EWG also noted that most cases did not have the IgG paraprotein typical of classical CLS.
- The EWG agreed that no updates to the SmPC or Risk Management Plan for COVID-19 Vaccine AstraZeneca were warranted based on the data presented and supported the proposal to keep the issue under review.
- 4. COVID-19 Vaccine AstraZeneca: Assessment of the draft protocol for a Post Authorisation Safety Study (PASS) to ascertain the incidence rate of adverse events of special interest
- 4.1 The VBR EWG was presented with an assessment of the draft protocol for a secondary database study in the VAC4EU (Vaccine Monitoring Collaboration for Europe) research environment to ascertain the incidence rates of adverse events of special interest in individuals vaccinated with COVID-19 Vaccine AstraZeneca.
- 4.2 The EWG agreed with the assessment of the study protocol and with the comments and lists of questions for the company proposed by the MHRA and the European Medicines Agency (EMA).

- 4.3 In particular, the EWG agreed with concerns raised about the proposed timelines for the study given the pace of roll out of the vaccine in the UK, and fully supported the proposal to ask the company to submit the first interim report and the statistical analysis plan (SAP) much sooner than had been proposed in the protocol. The EWG also recommended that the company should be asked to provide further information about when the study will start; information that had not been included in the draft protocol.
- The EWG discussed the limitations of the cohort study design which the company proposed to use as the primary study approach. The EWG supported the concerns raised regarding the likely issues with finding concurrent controls for the cohort study as more unvaccinated individuals become vaccinated with time. The EWG discussed the company's rationale for proposing the cohort design as the primary approach (that the self-controlled risk interval (SCRI) design is less able to study outcomes with a gradual onset, such as multiple sclerosis and peripheral neuropathies) but agreed with the assessment that these difficulties could be overcome by using the date of onset of first symptoms as the index date rather than date of diagnosis, and by studying a range of different risk intervals. The EWG supported proposals to make the SCRI design rather than the cohort design as the primary study approach.

The EWG further suggested that the company be asked to consider a more sophisticated statistical approach to the SCRI design, for example by modelling exponential decline in risk rather than specifying 'at risk' and 'not at risk' periods.

- In addition, the EWG expressed concerns as to whether data on individuals taking immunosuppressants and individuals living with HIV would be adequately collected in the study. The EWG questioned whether this information was captured in the two non-UK databases proposed by the company to be used in the study, noting that information about use of immunomodulators other than methotrexate would not be captured in CPRD (the 3rd database to be proposed for the study) and was not readily available from other sources in the UK. Similarly, information about individuals living with HIV would not be adequately captured in CPRD. The EWG suggested that these data may be more readily available in other European countries. The EWG recommended that the company further explore the availability of data on immunosuppressed individuals and those living with HIV in the databases currently proposed for the study and if necessary, to include additional European databases in the study to ensure that the safety of the vaccine in this important group of individuals can be evaluated in the study. If adequate data are not available, this should be included as an important limitation of the study in the protocol.
- The EWG noted that only 3 databases had been selected by the company for the study. To increase the power of the study and yield more meaningful data, the EWG suggested that the company be requested to select a number of additional European databases for the study.

5. Brief Update on COVID-19 Vaccines

The VBR EWG was updated on the progress status of each of the vaccines under review or to be evaluated in the future. Regarding the SPC for the Janssen vaccine, the EWG agreed with the company proposal to include 'Patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2)' as a warning in section 4.4 rather than a contraindication in section 4.3.'

6. Any Other Business

6.1 None.

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

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 17**th **May** at **5.15pm**.

The next scheduled meeting is to take place on Friday 21st May at 2.30pm.

The Meeting today started at 10:34 and ended at 12:32.

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 N	<i>l</i> lembers
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	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
	I to all meetings, receives all papers and presentations and is permitted full pation 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
•	e invited to all relevant meetings, receives all papers and presentations and is ted to participate in discussions when invited by the Chair. Does not contribute to

١ conclusions and recommendations

Observers

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

Annex II

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 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).

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).

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.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

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).

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 - <u>NPNS</u> 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).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – <u>Other relevant interests</u> 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.