

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

Minutes of the meeting held on **Monday 26th April 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor G Dougan
Professor N French
Dr A Riordan

Invited Expert

[REDACTED]*

Observers

[REDACTED]
Professor W S Lim

[REDACTED]
msav
[REDACTED]

Secretariat

[REDACTED]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenters supporting specific items*

[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - VRMM

MHRA Observers

[REDACTED] - LD
[REDACTED] - VRMM
[REDACTED] - LD
Dr S Branch - VRMM
[REDACTED] - MHRA-NIBSC
[REDACTED] - VRMM
[REDACTED] - MHRA-Policy
[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - Comms
[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - LD
Ms N Rose - MHRA-NIBSC
[REDACTED] - MHRA-NIBSC
[REDACTED] - LD
[REDACTED] - VRMM
Mr P Tredunno - VRMM
[REDACTED] - LD

[REDACTED]

4th February 2022

Key

LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control

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 and Dr Riordan for this meeting.

1.5 The Chair welcomed Invited Expert, Dr [REDACTED] from UK Health Security Agency (HAS) who presented item 2 - Update from UK HSA on Safety for AZ Vaccine.

1.6 The Chair welcomed the following observers:

Mr [REDACTED]
[REDACTED]

Dr [REDACTED] Joint Committee on
Vaccination and Immunisation, UK HSA

Professor [REDACTED]
[REDACTED] JCVI

Dr [REDACTED] Public Health Agency

Professor Wei Shen Lim
Chair of JCVI

Dr [REDACTED]
Public Health Scotland

Dr [REDACTED]
UK Health Security Agency

Dr [REDACTED] Public Health Wales

NOT FOR PUBLICATION

[REDACTED]
National COVID-19 Vaccination Programme

2. Update from UK HSA on Safety for AZ Vaccine

2.1 UK HSA England, AZ safety item 26/04/2021

The EWG heard a presentation from Professor [REDACTED] of UK Health Security Agency (UK HSA) on estimations of rates of vaccine-prevented COVID-19 cases, hospitalisations, ICU/HDU admissions and deaths. The rates of benefit were based on a wave equivalent to that of the second wave and the analysis was stratified by age and risk group status. The benefit data was based on a complete vaccination course (two doses) of the AstraZeneca Vaccine. The EWG heard that the data and calculations presented on vaccine effectiveness assumptions were largely based on data from the second wave scenario.

2.2 The EWG asked for further detail on the QCOVID score, and how this was used to benchmark rates of risk. The QCOVID data was used as one form of cross checking / data validation, and for comparison of risks between wave one and wave two. The EWG heard the QCOVID calculator computes a combination of risk of infection and the subsequent risk of acquiring a complication (if infected), in other words an absolute population risk during the 12 weeks during the first wave. The EWG also heard the rates used in the data analysis to calculate risk are available to the group for reference.

2.3 The EWG heard that projection modelling of a potential third wave is on-going. Currently, the model estimates third wave hospitalisation rates will be approximately 50% of second wave rates. The data period inputs for the model cover the first and second waves, and presently, but lack data on emerging variant strains. The current model is therefore limited in terms of its predictive accuracy in a situation where new strains may result in substantial differences in protection from the vaccine. The EWG also heard that the uncertainty level in the modelling was already very high but may improve when further data are inputted.

2.4 The Chair thanked [REDACTED] and the other contributors for the clear presentation on what is a complex subject.

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

3.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 21 April 2021. The data lock point for the Janssen vaccine was 12 April 2021. A summary of regulatory actions taken by the EMA and FDA since the last EWG meeting on 19 April 2021 was also presented.

3.2 Concerning the AstraZeneca COVID-19 vaccine, 2 recent draft publications on causal mechanisms and 4 published case reports were presented. The papers by [REDACTED] team on potential mechanisms suggested that the underlying causes of thromboembolic events with thrombocytopenia in Covid-19 infection were different to those following vaccination and the proposed sequence of pathophysiological events involving neutrophils was interesting and could support causality. However, some of the data on excipients was speculative and the published versions of the draft articles may contain additional information. The data presented would also require independent verification

NOT FOR PUBLICATION

- 3.3** An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including a summary table of the 4 reported cases after a second dose. Four of these cases were probable or possible, two of them tested negative for PF4 antibodies and the results are awaited or unknown in the 2 other cases. Additional follow-up clarified that a case was wrongly reported as occurring during pregnancy as we have not received any thromboembolic events with thrombocytopenia in pregnancy associated with the vaccine. The overall case fatality rate for all doses is stable at 20%.
- 3.4** The EWG was also given an overview of available outcome data for all confirmed cases. It was noted that the majority of cases were not associated with significant comorbidities that might be expected to limit function or quality of life before vaccination. However, the data on residual disability is limited as pre- and post-vaccination status has not been assessed using validated outcome measures and neurological deficits can recover after a year or more. UK haematologists are collecting long-term outcome data alongside HaemStar and the MHRA may receive this data.
- 3.5** The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The FDA has lifted the recommended pause on Janssen COVID-19 vaccine use after its safety review identified 15 cases of thrombosis-thrombocytopenia syndrome following the administration of more than 6.8 million doses.
- 3.6** The estimated number of second AstraZeneca COVID-19 vaccine doses administered has significantly increased to 4.4 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 22 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 5-year intervals and by gender. The overall incidence rate is 9.3 (8.1, 10.7) per million for first/unknown doses and the overall fatal incidence rate is 1.8 (1.3, 2.5) per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups.
- 3.7** The EWG considered the following 3 questions:
- 3.7.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?**
- The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive. However, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation, the benefits of immunisation in individuals aged under 30 years may be outweighed by the potential risks.
- 3.7.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?**
- The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reassuring but limited so the MHRA should continue to monitor second dose cases closely.
- 3.7.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?**
- Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action.
- 3.8** In conclusion, the EWG did not identify any potential trigger for urgent regulatory action.

4. **Any Other Business**

None.

5. **Date and time of next meeting**

The next meeting is scheduled to take place on Friday 30th April at 13:00.

The Meeting today started at 17:18 and ended at 18:33.

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

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.

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).

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 Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS 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 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).

NOT FOR PUBLICATION

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).

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 – 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

Professor [REDACTED]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [REDACTED]

Dr [REDACTED]