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

Minutes of the meeting held on **Tuesday 6th April 2021** at **12:00** 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 H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
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 P Shah

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted]
Ms R Arrundale - MHRA-Policy
[redacted]
Dr S Branch - VRMM
[redacted] - Comms
Dr SP Lam - LD
[redacted] - LD
Dr J Raine - MHRA CEO
[redacted] - MHRA-NIBSC
[redacted]

[redacted]

4th February 2022

Key

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

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 Professor Shah for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] Statistician, Public Health England

[redacted] Joint Committee on Vaccination and Immunisation, Public Health England

[redacted] NHS England [redacted] for COVID-19 Immunisation [redacted]

Professor Wei Shen Lim
Chair of COVID-19 Subcommittee at JCVI

[redacted] Public Health England

[redacted] Public Health Scotland

[redacted] Public Health England

[redacted] Vaccine Preventable Disease Programme at Public Health Wales

[redacted]
National COVID-19 Vaccination Programme

[redacted]
Public Health England

[redacted]
Public Health England

1.6 The Chair welcomed the following representatives from AstraZeneca:

[redacted] Late Respiratory & Immunology

[redacted] Clinical Development, Immunology

[redacted] Clinical lead

[redacted] Medical and Payer Evidence Strategy, Respiratory and Immunology

[redacted]
Professor of Haemostasis and Thrombosis, [redacted]

[redacted] Pharmacovigilance [redacted]

[redacted] Regulatory Affairs

[redacted] Medical Officer

[redacted]
Regulatory Affairs [redacted]

[redacted] Regulatory Science [redacted] Inflammation Autoimmune, Infection & Vaccines

[redacted] Pharmacovigilance [redacted]

[redacted] Patient Safety

2. Presentation from AstraZeneca

2.1 The company gave a presentation on the global reports of thromboses with concurrent thrombocytopenia. The company highlighted that the vast majority of cases had come from the UK and EU, and that there had been a significant rise in reporting following media interest. It was commented that CVST represented a significant number of the cases of thromboembolism reported, and the cases showed a trend towards younger age groups and females. The meeting was informed that a number of the cases had significant missing data which limited assessment.

2.2 The company presented their observed-expected analysis using a large US insurance claims database to calculate the background incidence of CVST, CVST with thrombocytopenia and any large thromboses with thrombocytopenia within a 14-day risk window. ICD10 codes had been selected which were considered to most closely relate to events reported in such cases. It was noted that the use of the US claims database had a number of limitations including a larger representation of the younger population and those who were insured which may not represent the population as a whole. The analysis showed that for thromboses with thrombocytopenia, there was a higher observed rate than expected in the younger age groups and that this imbalance was not seen in the older age groups (50+ years), and this was similar in the UK and EU data. Similarly, for CVST alone, there was a higher reporting rate in the observed cases than expected for those aged less than 60 years, but no increased incidence detected in those over 60 years old. It was noted by the company that confidence intervals were wide, and the number of cases was small.

2.3 The company concluded that the benefit risk balance for the vaccine remained positive. The company stated that they were working on epidemiological analysis alongside investigation into the mechanism of the events in association with the vaccine.

2.4 The EWG agreed that a consistent definition to use globally could be preferable, including which risk window should be considered. The company noted that there is a natural background incidence of anti-PF4 antibodies in the population regardless of heparin exposure and without thrombus associated, at around 3-5%. Analysis of sera from sample study participants was underway by the company to investigate the prevalence of anti-PF4 antibodies. The company confirmed that they were not aware of any cases occurring after the second dose.

2.5 The company confirmed that the study in adolescents had been paused for recruitment following a data monitoring board discussion.

2.6 The EWG commented how unusual it was to have a large usage of the vaccine in India and yet only 2 cases outside of Europe. The company confirmed that they were working with the Serum Institute of India to engage with national reporting work in India.

2.7 AstraZeneca representatives were asked to leave the meeting before the next presentation.

3. Thromboembolic events with thrombocytopenia - update on cases

3.1 The EWG was presented with an update of the Yellow Card data on cases of thromboembolism and thrombocytopenia 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 thromboembolism events. The EWG heard that the quality of cases had greatly improved since the introduction of the Yellow Card proforma with specific questions on tests and investigations.

3.2 Incidence rates of the events by age group were also presented to the meeting, alongside epidemiological data on the vaccine's impact on reducing COVID-19 cases, long COVID, hospitalisations, ICU admissions and deaths. Modelling data was also provided showing the impact of a hypothesised 10% slower roll out of the vaccine on the predicted cases in the UK.

3.3 The EWG discussed the incidence rates by age for both CVST and non-CVST events and fatalities. It was commented that the case numbers were low considering the usage. Differences compared to the company analysis of benefit risk were highlighted and this could be due to different calculations on the expected impact of the vaccines in preventing cases globally. The EWG noted that the data had consistently showed a higher incidence in younger individuals in both the MHRA and company data. The EWG concluded that it was important to communicate on the available evidence in the younger age groups and allow informed consent, but that an age cut off for usage would not be proposed at present from a regulatory perspective.

4. Proposed revisions to product information

4.1 The EWG was presented with proposed product information statements which had been compiled following discussion at CHM. The EWG agreed with the proposed contraindication wording for patients with previous major thrombotic event with thrombocytopenia. The EWG discussed the proposed warnings and description of symptoms. and generally agreed that the information proposed was appropriate. There was discussion on the time frame for the symptoms of concern and it was agreed not to be restrictive on this. The EWG considered a statement on the causal relationship should be maintained with consideration to the wording to reflect current evidence levels.

4.2 Advice on use in pregnancy was also discussed, noting the lack of data in this area and the desire not to restrict options for pregnant women when the risk factors were unclear. The EWG concluded that the current statement should be retained with a linking statement to the information in 4.4 and 4.8.

4.3 The draft statement for section 4.8 was presented and the limitations of the frequency definitions used were discussed as the "very rare" category did not clearly indicate the rarity of the events.

4.4 The EWG was informed that statements for the patient information leaflet would be drafted once the healthcare professional information had been confirmed and that lay members would have the opportunity to input on this.

5. Any Other Business

None.

6. Date and time of next meeting

The next meeting is scheduled to take place on Monday 12th April at 11:00.

The Meeting today started at 12:01 and ended at 14:38.

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 - 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).

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 – 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).

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).

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 – 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 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.

[redacted] **-** Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, [redacted] supported respiratory vaccine development activities at Janssen (Johnson & Johnson). [redacted] has now left that role.

[redacted] - Other relevant interests in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

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