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

Minutes of the meeting held on **Thursday 18th March 2021** at **10:30** 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
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson
Professor P Shah
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Ms S Hunneyball
Professor H J Lachmann
Dr A Riordan

Invited Experts – Presenters of Item 2

[redacted]

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted] - LD- Medical Writer
[redacted] - LD- Medical Writer
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] LD
[redacted] - LD
[redacted] LD
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] LD
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted]

19th July 2021

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

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts 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 at **Annex II** to the minutes.

1.4 Apologies were received from Professor Lachmann, Dr Riordan and Ms Hunneyball for this meeting.

1.5 The Chair welcomed the following invited experts for the meeting today:

Dr [redacted]
Consultant Epidemiologist, Public Health England

Dr [redacted]
Institute of Health Informatics

Dr [redacted]
Public Health Registrar at UCL

1.6 The Chair welcomed the following Observers for the meeting today:

Dr [redacted]
[redacted], Public Health England

Dr [redacted]

Dr [redacted]
HSCNI

Dr [redacted]
Public Health Scotland

Dr [redacted]
Public Health England

Dr [redacted]
[redacted] Public Health Wales

Dr [redacted] MB ChB, FRCGP, FIMC (RCSEd), DUMC
Clinical Workstream – [redacted]
National COVID-19 Vaccination Programme
NHS England and NHS Improvement (National)

2. Vivaldi Project

2.1 The EWG viewed slides and heard a presentation by Birmingham University/University College London (BHU/UCL) experts on the findings of the Vivaldi Project. The Vivaldi project is an ongoing prospective cohort study of staff and residents 65 years and over in care homes in England that analyses vaccine effectiveness against Polymerase Chain Reduction (PCR)-positive SARS-CoV-2 infection.

2.2 The EWG heard that analysis data are sourced from NHS Foundry (Pillar 1 and Pillar 2 for PCR testing data, and the National Immunisation Management Service [NIMS] database for vaccination). The primary outcome was any new PCR-positive SARS-CoV-2 infection, excluding any PCR+ within 90 days of a prior PCR positive (and start of time at risk delayed until 90 days had elapsed). The analysis period was 08 December 2020 to 09 March 2021 (the date of first vaccination in the resident cohort being the start date of analysis). Vaccination status was defined as a time varying exposure extending from unvaccinated, and day intervals up to 48^{+} days.

2.3 The EWG heard that the cohort for analysis was 10,101 residents (with a median age of 86). 88% of the cohort had received their first vaccine (2/3 Oxford/AstraZeneca and 1/3 Pfizer), with 11% of vaccinees having a prior infection. Only 6% had received their second dose; hence this cohort was not considered in this vaccine effect analysis.

2.4 The majority of the PCR testing in the analysis was Pillar 2 testing (99.4%) with only 0.7.% symptomatic at the time of testing. The median PCR results per month (1.6. PCR^{+} results) were predominately from Pillar 2 testing (84.7%), with only 7.6% symptomatic at time of testing. Based on this analysis data, the overall crude infection rate was 21.2/10,000 person day (95% Confidence Interval [CI] 20.1, 22.3). Overall, there was 52% PCR positives, with cycle threshold of less than 25 (Ct <25).

2.5 The EWG heard that analysis based on adjusted hazard ratios shows an early protective effect that may be due to the deferral effect with active outbreak, with a true protective effect likely from Day 28 for both vaccines. It was noted that the early deferral effect was greater with the AstraZeneca vaccine than with Pfizer; the expert explained that it was not clear as to why this was and suggested that it may be linked with the time of deployment of the two vaccines and the type of homes where they were deployed. Based on the results of the analysis of vaccination effect by prior exposure (infection), it is unclear as to whether vaccination is providing any protection beyond that gained from prior infection.

2.6 The EWG heard that future analyses will include sensitivity analyses and further exploration of Ct values data, further analyses of serology data from pre-and post-vaccination samples, vaccine effectiveness against hospitalisation due to COVID-19, vaccine effect after second

dose of vaccine, incorporating estimates of care home seroprevalence prior to vaccination into care home level analyses, and incorporating staff vaccination coverage estimates into future models.

2.7 The EWG asked for clarification as to the reason for the small number of residents (3 residents out of 631; 0.5% of the cohort) having different first and second vaccines. The external expert explained that this was unclear; however, this is as the NIMS records indicate.

2.8 The EWG asked the external experts whether vaccine protection in this cohort was being seen at 28 days, later than in other studies, due to the older population and the slower ability to mount an immune response in this population. The experts stated that the reasons were unclear. However, they explained that mainly Pillar 2 testing was analysed where the subjects were likely asymptomatic, while the outcome in the trials was symptomatic infection, although these trials looked at some asymptomatic cases as well. External experts also commented that the onset of symptomatic disease appears slightly later in the elderly population than the younger age groups, around 21 days versus 14 days. It was agreed with the EWG that this was consistent with data that has already been published.

2.9 The EWG questioned whether the stratification of data by care home should be carried out to reflect the status of other residents in the care home. However, the external experts explained that in the majority of cases the vaccination is carried out too rapidly within a single care home for this effect to be analysed and adjusted for through this type of stratification.

2.10 The EWG asked whether the invited experts could provide an explanation for reported deaths in unvaccinated care home residents only, in terms of survivor bias. The invited experts commented that potential biases (e.g. decisions as to which residents are vaccinated or are hospitalised due to end of life care) make it difficult to analyse the outcomes of hospitalisation and death; however, a sensitivity analysis is planned to exclude those who were never vaccinated, but were at the home at the time vaccination was occurring within the care home.

2.11 The EWG commented that they are looking forward to the analysis on the impact of the second dose. The external expert confirmed that analysis would be conducted on the second dose once the data is available.

3. Pfizer/BioNTech COVID-19 Vaccine – Risk of severe cutaneous adverse reactions (SCAR)

3.1 The EWG was informed of two reports of Toxic Epidermal Necrolysis (TEN) in which the suspected reaction occurred following vaccination with the Pfizer-BioNTech COVID-19 vaccine, one of them fatal, and one case of Stevens-Johnson syndrome (SJS). The EWG noted that SJS and TEN are variants of the same condition distinct from erythema multiforme with an incidence of about 1-2 cases per million population per year. The EWG was reminded of clinical and histopathological features of this condition.

3.2 The EWG considered an assessment of clinical trial data and individual case reports received via the UK Yellow Card Scheme for the Pfizer-BioNTech vaccine concerning Severe Cutaneous Adverse Reactions (SCARs), including cases of SJS/TEN.

3.3 The EWG agreed that the currently available data do not provide evidence of a causal association between Pfizer-BioNTech vaccine and SJS/TEN, and in the fatal case presented concomitant medication could have also triggered the reaction. In all three cases, the onset of symptoms was inconsistent with a vaccine related effect. In addition, the clinical and histopathological features reported in these cases did not meet all the diagnostic criteria for

SJS/TEN with regard to both clinical and histopathological features. The EWG also noted that the number of cases does not exceed the background rate expected for this disease given over 10 million doses of vaccine were administered.

3.4 The EWG agreed that the review of other bullous and erosive skin conditions reported via the Yellow Card scheme did not identify any further possible cases of SJS/TEN and considered no other cases of Severe Cutaneous Adverse Reactions included in the review raised a concern.

3.5 The EWG noted that reviews of less serious skin hypersensitivity reactions (including rash, urticaria, pruritus) and delayed hypersensitivity reactions (including those starting at the injection site) are ongoing in parallel and agreed these should be discussed at the meeting only if a concern emerged.

3.6 The EWG advised that based on the data currently available no update to the product information is required, but that the risk of severe cutaneous adverse reactions should continue to be kept under review.

4. Any Other Business

4.1 None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Wednesday 24th March 2021 at 13:30.

The Meeting today started at 10:31 and ended at 11:28.

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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 - 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.

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 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).

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.

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

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.

Observer declared interest for this meeting

Dr [redacted]