COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP - Quality ad hoc Group

Minutes of the meeting held on **Thursday 17th December 2020** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor H J Lachmann

Members of the CTBV Expert Advisory Group

Professor B K Park

Apologies

Professor M Turner

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

MHRA Observers

Ms R Arrundale - Policy
[redacted] - VRMM
Dr S Branch - VRMM
Dr P Bryan - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] _ VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe[1]
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

[redacted]

18th January 2021

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

[1] Joined during item 2

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines

1. Introduction and Announcement

1.1 The Chair reminded Members 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 The following members, invited experts and observers declared interests and other relevant interests for this meeting:

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 joining 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 reference 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 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 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.

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

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitatve Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne 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 Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed:

Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

1.5 Apologies have been received from Professors Lachmann and Turner for this meeting.

2. Pfizer/BioNTech new batches

2.1 The EWG heard an update on the new batches of Pfizer/BioNTech vaccine considered for release.

2.2 The EWG discussed the low level of RNA integrity in the Emergency Use (EU) batches and why they are lower than that seen in the CT batches as there appears to be no clear reason for this difference. The EWG considered shearing (non-intact RNA particles) as a possible reason for the low RNA integrity. The EWG heard that the EU batches are close to the edge of failure at release in terms of the RNA integrity specification. The EWG heard that RNA integrity decreases with decreasing stability. The EWG considered whether a loss of RNA integrity will lead to a reduction in immunogenicity.

2.3 The EWG heard that data from NIBSC on batch release has been more consistent than that provided by the company. The EWG heard that NIBSC have reported higher potency for EE and EK batches than the company reported. The EWG discussed possible issues with regard to the potency assay the company are using. [redacted]

2.4 The EWG heard that MHRA and NIBSC will contact PHE with regard to batch testing for immunogenicity.

2.5 The EWG agreed that batches EE and EK could be released, however, as concerns have been noted liaison with PHE is important to evaluate whether immunogenicity testing can be performed on the batches.

3. Update on BNT162b2 risk of anaphylaxis

3.1 The EWG discussed how to bench mark the numbers of reactions and compare to the number of reactions seen following flu vaccination. The EWG considered the rates of anaphylaxis in the community and the following paper was referenced which showed that rates of anaphylaxis are lower in those aged 65 years and over: https://www.sciencedirect.com/science/article/pii/S0091674902001641?via%3Dihub

3.2 The EWG agreed that Professor Solomon should liaise with VRMM to ensure that neurological events are collected properly and to evaluate whether any such events are related to the vaccine or not.

3.3 The EWG agreed that individuals who had mild AEs following their first dose should still take their second dose but that the monitoring post dose should be increased to half an hour. The EWG agreed the company should be asked whether any individuals who had mild events following the first dose have had issues following their second dose.

3.4 The EWG heard that an expert from the allergy community may join Vaccine BR EWG in next few weeks.

4. AZD1222 Clinical Assessment Report – Efficacy

4.1 The EWG heard an update on the efficacy aspects of AZD1222. The EWG heard that broadly MHRA has received all efficacy data required now.

4.2 The EWG heard that WHO criteria are met in terms of efficacy; however uncertainty remains around the level of dose and timing between the two doses. More information on the dosing interval is expected from the company on 22 December 2020. The EWG noted that the subset for efficacy is a relatively small proportion of the whole population and there is a need for assurance that the data seen is reflective of the overall data. The EWG agreed the company should be asked how many events are awaiting adjudication in study COV001 and COV005. The EWG agreed MHRA should perform a tipping analysis to see if the WHO criteria are still met in a worst-case scenario. The EWG heard that the company have not performed an analysis including these 2 studies as the SAP stated they would not include any study that had less than 5 Covid-19 cases. However, the EWG agreed the company can be asked to provide the data on these events.

4.3 The EWG noted there is no information yet on asymptomatic transmission. The EWG heard that the asymptomatic analysis the company have provided is not adequate and MHRA have requested an analysis on all cases (symptomatic, asymptomatic and no disease together) and not asymptomatic cases in isolation.

The EWG discussed the lack of data on severe cases of Covid-19 and the lack of data in the elderly. The bulk of efficacy data is in the 18-55 years of age group. A subgroup analysis in the group 18-55 years vs the group > 55 years should be requested from the Company. The EWG agreed to return to the issue of age once these data are received.

4.4 The EWG discussed the disconnect between immunogenicity (antibodies and T-cells) and efficacy. The EWG noted that in terms of immunogenicity there is not much difference between the LD/LD and SD/SD groups, nor between age groups.

4.5 The EWG agreed that as the vaccine contains polysorbate the company should be asked for further details around the cases of anaphylaxis that occurred with the AZ vaccine. The EWG heard further safety data (e.g. narratives and listings) will be received 21 December 2020. The EWG heard that over 1000 cases are in the age range 65 years and over for the safety data.

4.6 The EWG agreed data gaps in racial diversity, efficacy in severe cases (due to limits in sample size), and seropositivity at baseline could be accepted although the company should be asked to address these points with the next efficacy analysis in the future.

5. AZD1222 Quality update

5.1 The EWG heard an update on the quality aspects of AZD1222. The EWG heard that data for the three Reg 174 batches are expected 21 and 28 December 2020 and 18 January 2021.

5.2 The EWG heard the quality data will be fully presented at the next EWG meeting 22 December 2020.

5.3 The EWG noted a lack of specifications such as infectivity. The EWG considered there does not seem to be an assay with regard to expression of the spike protein. The EWG heard the [redacted] assay was only used for characterisation and not as a release assay. The EWG agreed to discuss in detail at the next EWG. The EWG heard that NIBSC have noted this with the company.

5.4 The EWG heard that NIBSC tests on the three batches for appearance, identity and the cell-based test were all in specification.

6. <u>Future Steps / Any Other Business</u>

6.1 Quality aspects of the Moderna vaccine

6.1.1 The EWG heard an update on the Moderna vaccine. The EWG was informed that the non-clinical dossier was almost complete. The company had provided sufficient results from the animal reproductive toxicology studies to allow the EWG to assess the potential use of this vaccine in pregnancy and during breast-feeding based on a benefit:risk consideration.

6.1.2 The EWG heard an update on the quality aspects of the rolling review of the Moderna vaccine. The EWG heard that the data received and reviewed so far is for product manufactured in the US; it was noted that product from US manufacturing sites will only be supplied to the US. [redacted]

6.1.3 The EWG heard that data for the first EU batch is expected Friday 18 December 2020. The EWG heard that currently this product is being assessed under a rolling review and a Regulation 174 has not been requested.

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

Tuesday 22nd December 2020 at 11:30

The Meeting started at 10:34 and ended at 13:18

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 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.