COMMISSION ON HUMAN MEDICINES (CHM)

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

Minutes of the meeting held on **Monday 7th 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 H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

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

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
Ms R Bosworth - COMMS
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC

MHRA Observers

Ms R Arrundale - Policy
[redacted] - VRMM
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC

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

Observer
Professor S Ralston (Chair of CHM)

Secretariat
Dr K Wydenbach - LD

[redacted]

[redacted]

18th January 2021

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
COMMS = MHRA Communication Team

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:

C19VBR

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 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 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 Quantitative 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.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
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.

CPS

Mr V'lain Fenton-May – 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)

2. Minutes of the Covid-19 VBR EWG meetings

2.1 COVID19VBR EWG Wednesday 18 November 2020 Draft Minutes

2.1.1 These minutes will be revisited after further amendments have been made.

2.2 COVID19VBR EWG Friday 20 November 2020 Draft Minutes

2.2.1 These minutes were approved as an accurate and true record of the proceedings.

2.3 COVID19VBR EWG Saturday 21 November 2020 Draft Minutes

2.3.1 These minutes were approved as an accurate and true record of the proceedings.

2.4 COVID19VBR EWG Tuesday 24 November 2020 Draft Minutes

2.4.1 These minutes will be revisited after further amendments have been made.

3. Update on Pfizer/BioNtech

3.1 The EWG heard an update on the Pfizer/BioNtech vaccine BNT 162b2. The EWG heard that 8 or 9 batches have been allocated to the UK.

The EWG discussed how variations in batches may possibly affect immunogenicity in patients. The EWG agreed batches should be checked to make sure they are immunogenetic. The EWG heard PHE are looking at serology of individuals that have been vaccinated. The EWG agreed it would be useful to compare serology between individuals who have received vaccine from different batches.

The EWG noted that the data from NIBSC was consistent and met the defined criteria but it was agreed that the specifications provided by the company were not adequate and they should provide proper lower and upper limits. If the specifications are not adequate it is difficult to reject bad batches. In particular, the [redacted] requires adequate upper and lower limits for the specification.

The EWG agreed that the definition of RNA integrity requires improvement and more detail on how it relates to immunogenicity. The EWG also noted that the cold chain has not been validated.

3.2 The EWG heard that each individual receiving vaccine will be given a little card with the brand and the batch number on it.

The EWG discussed the public perception on the release of emergency use batches. The EWG heard that batches can be rejected if they are not satisfactory and then it will fall to the company to provide replacement batches, but it would not be known when replacement batches would be provided. The EWG agreed that the release of further batches is at the discretion of MHRA and does not need EWG or CHM approval.

3.3 The EWG heard that dose response studies have been performed with the vaccine and some response was observed between the 10 and 30 microgram dose (18-55 years age group) but the response was flat between the 20 and 30 micrograms dose (18-55 years age group). A stronger response was seen between the 20 and 30 micrograms dose in the 65 – 85 years age group. This suggests batch variability is likely to have less of an effect.

3.4 The EWG heard that some of the instructions for use are causing issues and MHRA staff are meeting with Chief Pharmacists to resolve these. The EWG heard that in terms of deployment the stability data the MHRA has seen has not changed and no further qualification has been provided by the company. The shelf-life remains 120 hours at [redacted] once removed from the freezer (undiluted), and no further information has been provided on the diluted vaccine. The breakdown of the packs is performed at [redacted] and the countdown with regard to shelf-life begins as soon as the vaccine comes out of the freezer. The stability data allows for two transportations by refrigerated lorry in two 6-hour transports (undiluted) in refrigerated conditions. Once major distribution has been achieved, the more distant deployment, for example to care homes and rural homes, is more difficult. Transport of vaccine via boat or plane has not been qualified. When the vaccine reaches a temperature above [redacted] the 'clock starts to tick' and all vaccine administration needs to be done within 120 hours. The EWG agreed deployment is not within the remit of MHRA.

The EWG agreed that MHRA can release the three batches of BNT162b2.

4. Update from Communications team

4.1 The EWG heard a summary on the communications plan. The EWG heard that any requests for interviews received by any member of the EWG should be refused and these requests forwarded onto the news centre at MHRA. The EWG discussed the comments made by the ex-Vice President of Pfizer. The EWG heard that the communications team will contact Pfizer with regard to this. The EWG heard that MHRA will be considering members of the EWG making comments on this vaccine and the process of authorisation in the future but at present the communications are being very closely managed.

5. AZD1222 update

5.1 The EWG heard an update on the assessment of the AZD1222 vaccine candidate. Three batches have been allocated to the UK.

5.2 The EWG agreed it is unlikely that any more data with regard to T-cell exhaustion can be gained unless any clinical signals are observed. The EWG noted it would be interesting to see if any hepatic toxicity signals are seen in the clinical trial data. The EWG agreed that information with regard to reproductive studies should be consistent with that for the Pfizer vaccine.

The EWG noted that the nonclinical package of data is all at one dose so there is no dose response data. The EWG agreed that any signals seen in the clinical data should be tracked back to the nonclinical data.

The EWG heard a summary of the assays from NIBSC.

The EWG heard the [redacted] evaluates [redacted] and [redacted] in cases of infection after vaccination, and the [redacted] method for the detection of antibodies (against COV-2 S, COV-2 N protein and COV-2 RBD) evaluates an immunogenicity response in convalescent sera. The EWG noted that a different package should be used for evaluating the immunogenicity response. The sample should not be from convalescence sera, it should be validated against the relevant characteristics of the population receiving the vaccine. The EWG agreed that the company should share how they validated the [redacted] that was used.

The EWG agreed the [redacted] is suitable for use to evaluate cases of infection after vaccination.

5.3 The EWG heard that only symptomatic patients were included in the primary analysis. A secondary endpoint is the incidence of asymptomatic cases as determined by weekly PCR tests on nose/throat swabs (in the UK COV002 study only)

The EWG discussed the low dose (LD)/high dose (SD) regimen used in the AZ/Oxford trials and whether this was intentional or not. The applicant is applying for a SD/SD dosing regimen (not the LD). Reports from Oxford state the LD was planned and AZ report it was a mistake. The EWG heard this does not affect how the results are interpreted.

The EWG heard that use of the LD was not intended. Depending on the product manufacturer the concentration of virus particles was measured using a different method, which explains the difference in the dose after the manufacturer was changed. This will be addressed in the next meeting.

The clinical studies COV001 and COV002 have been inspected by MHRA Inspectorate. No critical findings were found for the first study, and the second inspection is ongoing.

The EWG heard that the LD was not planned from the beginning of the study, but when the sponsor became aware the trial was still unblinded, they reacted, and a protocol amendment was included to introduce the LD.

The EWG heard the primary efficacy population analysis was young (median 40 years, 60% female, 450 subjects ≥ 70 years), a much younger population than for the Pfizer vaccine. For the LDSD group, patients were 18-55 years of age with a median of 40 years age.
The EWG heard that the applicant has planned efficacy analysis by BMI and comorbidity, this data is expected.

The EWG discussed how priming with a small dose followed by a large dose can achieve a better response, may be due to immune memory which can give a stronger booster effect. It is also possible that it may be due to a lower neutralising antibody response to the ChAdOx1 vector itself, which may allow for a better anti-Spike response to the booster dose. The EWG agreed it would be useful to have immunological responses to the ChAdOx1 vector itself.

The EWG heard that data have been published in the last Lancet paper which reported the anti-ChAdOx1 response is lower with the lower dose which may be part of the reasoning.

5.4 The EWG heard the applicant has not provided an explanation of why a saline placebo was used for the South African study and a meningococcal vaccine for the other 3 studies.

6. Moderna update

6.1 The EWG heard an outline of the quality, non-clinical and clinical data submitted so far. The EWG also heard about the expected timing and content of future submissions.

The EWG heard that a Regulation 174 letter may be received this year; a national marketing authorisation is not legally possible before 01 January 2021. A Regulation 174 approval before 01 January 2021 could be feasible if the Company submits the data according to the plan shared with the MHRA, and no major issues arise on assessment. The EWG considered whether a less urgent approach would be more appropriate as the UK is unlikely to receive product before Spring 2021.

The EWG heard that following an urgent meeting with the company 3 days ago, MHRA was informed that a batch may be available for the UK before the end of this year.

The EWG heard that NIBSC has not yet seen any material for this vaccine yet and therefore if a Regulation 174 letter is received NIBSC would only be able to present a very sparse study plan for this vaccine.

The EWG heard that MHRA will provide an update of submission and assessment timelines in the near future.

6.2 The EWG heard that the applicant will provide MHRA with any questions/responses they have received/submitted to the EMA. The EWG heard that the applicant has performed a general toxicity study that is non-GLP and that this was agreed by the EMA. The EWG noted that the nonclinical AR will be shared with the committee in the near future.

7. Future Steps / Any Other Business

7.1 Members were reminded that:

The content of papers and proceeding of the meeting are strictly confidential and should not be disclosed.

All enquiries, approaches, interview requests and requests for comments made directly to the members from the media or stakeholders, verbal or written, should be declined and referred to the agency's news centre in the first instance.

7.2 The Secretariat informed the Group that we may be moving over to a new platform 'Microsoft Teams' for future meetings of the EWG.

8. Date and time of next meeting

Thursday 10th December 2020 at 14:30

The Meeting started at 10:36 and ended at 13:36.

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.