COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 24th 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
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors[1]

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items[1]

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

MHRA Observers

Ms R Arrundale - Policy
Dr S Atkinson - Dir
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
Ms T Moore - IE&S
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr J Raine - MHRA CEO
Dr N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC

[1] supporting specifc items [redacted] - LD

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
Dir = Director of Operational Transformation
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards

[redacted]

22nd January 2021

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 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

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 were received from Professor Shah for this meeting.

2. AZD1222 Deployment Model (For information)

2.1 The EWG heard that NHS England have supplied a one slide framework which is similar to the Pfizer/BioNTech vaccine but without the cold storage temperature requirements. The models for all the home countries are ready but the slide decks have not yet been supplied. The EWG heard they are likely to be similar to that supplied for NHSE.

2.2 The EWG heard there is a roving model, so the vaccine can be supplied to nursing homes and private homes. The EWG agreed stability will be important with regard to the roving model.

3. AZD1222 Quality assessment - update

3.1 The EWG heard an update of the quality assessment and NIBSC testing of AZD1222.

3.2 The EWG heard that AZ have complied with the MHRA request to reduce the in-use shelf-life to 6 hours, and this has been reflected in the product information which is now complete from a quality point of view.

3.3 The EWG heard that all testing by NIBSC for batches AB0001, AB0002, AB0003 falls into specification and NIBSC are prepared to issue certificates. The EWG heard that NIBSC are content with the performance of the potency assay.

3.4 The EWG heard that each batch contains approximately 450,000 doses.

3.5 The EWG noted that in this case we are not checking against approved specifications, we are comparing against clinical trial batches. This is valid but must remember it is not usual procedure. The EWG agreed it is important to ensure continuity between clinical trial batches and commercial batches. The EWG noted that specifications will be tightened in time.

The EWG heard there are outstanding other concerns which the company should respond to by mid-January 2021. These responses are not required to reach a decision for this batch. The EWG heard there are no major concerns relating to this batch for a Regulation 174.

The EWG were reassured that the [redacted] have GMP certification in place and have sufficient experience in manufacturing vaccines/sterile products. They have a manufacturer import authorisation (MIA) in place which covers this process. The EWG heard that media fill data have been supplied to show the site can produce product aseptic product. No specific validation is required as it is fulfilled in the matrix.

The EWG heard a second batch for this vaccine will be submitted by Monday 28th December 2020. The EWG agreed they only need to see data on this batch if there are any concerns. The EWG endorsed the quality data presented and agreed with the Regulation 174 proposal with regard to the quality aspects.

4. Non-clinical update on AZD1222 – reproductive toxicity focus

4.1 The EWG heard an update with regard to the non-clinical aspects of AZD1222.

4.2 The EWG heard the preliminary reproductive toxicity study has been completed in mice and no major issues arose.

4.3 The EWG discussed the reproductive toxicity and the precautionary text that should go into the SmPC as the animal data is not yet complete. The EWG discussed whether the text should be aligned with that for the Pfizer/BioNTech vaccine.

4.4 The EWG agreed with the wording 'The full relevance of animal studies to human risk with vaccines for COVID-19 remains to be established.'

The EWG agreed that for pregnant women where the risk of not having the vaccine is greater than the risk of having it, a clinical decision will need to be made.

4.5 The EWG discussed how long the adenovirus/drug substance persists in the body and heard this will be addressed by the company in a kinetic study for up to 29 days. The expectation is distribution will be local and that, in principle, the exposure should decrease over time. The EWG endorsed the non-clinical data presented.

5. Verbal update on AZD1222 clinical data

5.1 The EWG heard an update on the clinical aspects of AZD1222. The EWG noted that comparisons of the low and standard doses are non-randomised comparisons and the apparent differences are likely to be because of confounding factors, such as dose interval. The confounding was generated by the low dose being given by error early in the trial, a

protocol amendment which affected the timing of the second dose, and older subjects being introduced late in the trial. The exploratory analyses suggesting improved efficacy with increasing dose interval are also subject to confounding but have support from immunogenicity data.

Overall, the EWG endorsed the efficacy assessment of MHRA.

5.2 The EWG discussed the lack of subjects aged 55 and over and aged 65 and over in the trial. The EWG heard that the best direct evidence of efficacy for those aged over 65 is looking at all cases following the first dose. The EWG noted that there is no hard data that immunogenicity drops in individuals at higher ages, over 55 years and over 65 years. The EWG discussed the risk of vaccine escape and vaccine evolution if the vaccine has low efficacy in vulnerable groups. The EWG also noted the risks of not vaccinating in these groups.

The EWG noted that more data in older populations is expected from future analyses. The EWG agreed that the trend suggests the vaccine would be efficacious in the older populations.

The EWG agreed the vaccine should be licensed in those over 18 years of age and discussed the inclusion of appropriate wording with regard to the lack of efficacy data in the older age groups.

The EWG noted there is precedent for giving licences to medicines with limited data in elderly patients, e.g. statins.

The EWG agreed the references to the low dose should not be included in the regulatory document (product information).

5.3 The EWG agreed that there is evidence that protection after a single dose is maintained up to 12 weeks after dosing. The EWG agreed that there is reasonable evidence that a longer dosing interval gives better protection after dose 2. The EWG agreed a dosing interval of 4-12 weeks with MHRA to decide the wording around this to indicate the likely better results with dose intervals 8-12 weeks before the EWG meeting on Tuesday 29th December 2020.

5.4 The EWG noted that public health need is part of the assessment in relation to a Regulation 174 procedure. The EWG heard that conditions of the approval can be changed and amended as more information becomes available.

5.5 The EWG heard that the committee agree the parameters for use of the vaccine and JCVI can only supply the vaccine in line with these parameters.

5.6 The EWG were in agreement with a broader indication with regard to age (individuals ≥18 years old).

The EWG agreed the term ‘demyelinating disorders’ in Section 4.4 of the product information, should be changed to ‘neuroinflammatory disorders’.

The EWG noted that AZD1222 contained the excipient polysorbate 80 which, rarely, has been associated with anaphylactic reactions. The EWG noted that polysorbate 80 is included in many biological products, including other vaccines. In particular, Fluad contains more than double the amount of polysorbate than this vaccine and Fluad is indicated in the over 65-year age group. The EWG agreed that the standard contraindication and warning in sections 4.3 and 4.4 regarding hypersensitivity/anaphylaxis in the product information was sufficient.

The EWG agreed that, currently there was insufficient evidence to recommend prophylactic use of paracetamol. However, the inclusion of wording in the product information regarding symptomatic use of paracetamol was supported.

The EWG discussed the potential risk of neuroinflammatory disorders, including the small number of cases observed in the clinical trials. It was agreed that a causal relationship has not been established between vaccination and these cases.

The EWG discussed vaccine associated enhanced disease and noted that the period of follow-up is too short to determine the risk, however, it was noted that VED is a theoretical risk which has not yet been observed in humans.

6. Dose interval discussion for BNT162b2 – Q from NHS/DHSC

6.1 The EWG discussed a slide presentation of a statistical analysis performed on data from the initial Pfizer submission in order to evaluate the efficacy provided by the first dose. The EWG agreed that the vaccine efficacy (VE) reported by Pfizer of 52.4% (95% Confidence Interval of 29.5 to 68.4) is likely to be an underestimate since little protection is expected within 14 days following the first dose. The EWG agreed that calculation of the efficacy of the first dose discounting COVID-19 cases in the first 14 days would be more accurate.

6.2 The EWG heard the Pfizer analysis of COVID-19 cases taken from the second dose to 7 days after the second dose is expected to be a better estimate of the efficacy of the first dose. This analysis estimated vaccine efficacy (VE) as 90.5% (CI 61.0, 98.9) based on 2 COVID-19 cases in the vaccine arm of the study compared to 21 COVID-19 cases in the placebo arm.

6.3 The EWG also discussed the results of the MHRA analysis of VE taken from interim raw data. This analysis found a VE of 91% (CI 63, 98) from day 14 to before dose 2 was given, based on 2 COVID-19 cases on vaccine compared to 23 COVID-19 cases on placebo. From Day 21 to before dose 2 was given there were no COVID-19 cases on vaccine compared with 8 COVID-19 cases in the placebo group. The EWG agreed that there was evidence that protection was strong at 21 days after dose 1 and was not declining at that point.

6.4 The EWG also reviewed a Tabled Paper submitted by PHE on an independent analysis of the full Pfizer data. This analysis found a VE of 89% (CI 52, 97) from day 15 to day 21 after the first dose based on 2 COVID-19 cases on vaccine compared to 18 COVID-19 cases on placebo. The VE increased to 91% (CI 74, 97) from day 15 to day 28 based on 4 COVID-19 cases on vaccine compared to 42 COVID-19 cases on placebo. The EWG agreed the data suggest there is no decline in the level of protection at 28 days and that there is no biologically plausible reason to expect that it would decline rapidly. Immunological principles and experience with other types of vaccines suggest that immunogenicity may be improved with more prolonged intervals between doses in the primary immunisation series.

6.5 The EWG were reminded of the condition of the authorisation that it must be ensured that two doses are given to each patient. The EWG agreed that immunologically there is no concern if the second dose of vaccine is from a different batch than the first.

6.6 The EWG considered the risks of a partially immunised community if the dosing interval is too long and individuals only take one dose.

6.7 The EWG heard that the ever-changing public health need can be taken into consideration when making a decision. The EWG agreed that the dosing recommendation should be ‘at

least 21 days apart' without specifying an upper bound. The EWG noted this is also in line with the EMA recommendation.

7. Moderna non-clinical assessment

7.1 The EWG heard an update on the non-clinical assessment of the Moderna vaccine. The EWG heard that there are no major objections.

7.2 The EWG agreed the company should provide more information on the pregnancy rates observed.

7.3 The EWG discussed the use of an alternative mRNA to that in mRNA-1273 in the tissue distribution study.

The study was conducted using mRNA-1647, and not mRNA-1273, the clinical product. mRNA-1647 is a novel vaccine that contains 6 distinct mRNA sequences. Since mRNAs that are within an LNP of the same composition (i.e. mRNA-1273 and mRNA-1647) are expected to distribute similarly, this approach is acceptable with the proviso that information on particle size and other factors that can influence the distribution of the LNP e.g. surface charge is provided to demonstrate that the two mRNA constructs are sufficiently similar to enable "read across" from MRNA-1647 to mRNA-1273.

Further information on their disposition, distribution, persistence and fate on the two novel lipid nanoparticles (SM-102 and PEG2000-DMG) should be provided since they have not been used previously in a pharmaceutical product.

The EWG heard that this vaccine has now been approved by the FDA.

7.4 The EWG endorsed the non-clinical questions posed to the company. The EWG agreed the overall package appears to be more extensive than the Pfizer one.

7.5 The EWG agreed that although there are some concerns, there are no major objections.

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

8.1 None.

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

Tuesday 29th December 2020 at 10:30

The Meeting started at 10:32 and ended at 14:41

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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.