COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 27th November 2020** at **14:45** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French[1]
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

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] LD
[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
Ms R Arrundale - Policy
[redacted] - Dir
Dr M Bailey - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] LD
[redacted] - Policy
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr SP Lam - LD

Observers - CHM

Professor S Ralston (Chair of CHM)
Dr J Fraser
Professor J Friedland
Professor R Gilson
Professor M Macleod
Professor S Meredith
Dr M Wilson
Mrs H Ward (Invited Expert of CHM)

[redacted] - VRMM
[redacted] – Government Legal Team
Mr K McDonald - LD
[redacted] - IE&S
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - LD
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - LD

Secretariat

[redacted]
[redacted]
[redacted]

Mr P Tregunno - VRMM
[redacted] - LD
[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
PHE = Public Health England
CHM = Commission on Human Medicines
DMO = Deputy Medical Officer
IE&S = Inspection, Enforcement & Standards
Dir = Director of Operational Transformation

[1] Joined at item 2

[redacted]
18th 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:

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 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.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

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.

Professor Turner – Other relevant 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. Certainly I don't 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

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.

Professor Friedland – NPNS - GlaxoSmithKline, Sanofi, Pfizer

Professor Gilson – NPNS - Pfizer, GlaxoSmithKline, Novavax, Janssen, Oxford University

Professor Macleod – NPNS - Sanofi, Pfizer, Janssen

Professor Meredith – NPNS - Janssen, GlaxoSmithKline, Pfizer, AstraZeneca, Sanofi The Unit in which Professor Meredith works at University College London is coordinating the Imperial Covid Vaccine trials, however Professor Meredith is not involved.

1.4 Apologies have been received from Professor Shah for this meeting.

1.5 The Chair welcomed:

Chair and Members of the Commission on Human Medicines (CHM)

Members of the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG)

Chair and Members of the Chemistry, Pharmacy & Standards Expert Advisory Group (CPSEAG).

2. The EWG heard a presentation on the non-clinical aspects of BNT162b2

2.1 The EWG heard that the company have not provided any reproductive toxicity information. There is nothing to suggest that the product is teratogenic but without data to support this, it cannot be known for certain.

2.2 The EWG considered that in the absence of all the necessary data a path forward may be to apply the same approach as that taken in the clinical trials. Physicians will require clear advice on what do if a pregnant patient requests vaccination.

2.3 The EWG agreed the proposed wording for Section 4.6 of the Information for UK healthcare Professionals document.

2.4 The EWG noted that a communications strategy will be required to ensure patients are informed around the advice for women of childbearing age, pregnant and lactating women before they present for vaccination.

2.5 The EWG discussed whether it may be necessary for women of childbearing age to do a pregnancy test before vaccination as per the clinical trial population.

3. Clinical aspects of BNT162b2

3.1 The EWG heard that the clinical assessment team have now received sufficient data to reach a position on the authorisation of use of the vaccine under a Regulation 174.

3.2 The EWG noted that the prioritisation with regard to vaccination would be in accordance with the guidance from JCVI. The EWG agreed that the prioritisation is supported by the clinical trial data.

3.3 The age range for vaccination was discussed taking account of the pivotal clinical trial. The EWG noted that the benefits of the vaccine were apparently lower for the younger age groups. In view of this and given the short period of time that the vaccine has been studied, the question was raised if use in subjects less than 50 years of age was justified; one member of the EWG considered that it was not. The EWG discussed and concluded that the risk / benefit of COVID-19 mRNA Vaccine BNT162b2 is considered to be positive in all subjects aged 16 years and over.

3.4 The EWG discussed the need for inclusion of additional wording in Section 4.4 of the Information for UK healthcare Professionals in relation to the use of BNT162b2 in subjects who had already received partial or full vaccination with another COVID-19 vaccine. It was agreed that additional wording should be included and considered wording around 'not to recommend' and 'no evidence'.

3.5 The EWG considered use of the vaccine in people with a clinical history of COVID-19 or in people with no history of clinical illness but serological findings of COVID-19 antibodies or antigens at least in one assay. While the percentage of subjects in the clinical trials who were seropositive or PCR positive at baseline was relatively small, the efficacy and safety data in these patients was comparable to that in seronegative subjects. The EWG did not consider past infection to be a risk for vaccination based on experience from other vaccines and therefore considered that the vaccine could be administered in these subgroups. The group recommended that the company be requested to evaluate these subgroups further in a post-authorisation effectiveness study. The sizeable population of HCPs who have previously had COVID-19 could contribute to such a study.

3.6 The EWG agreed that Section 4.5 of the 'Information for UK healthcare Professionals document' should contain information on concomitant vaccination. Participants in the pivotal study were excluded from the receiving the flu vaccination 14 days prior or 14 days after vaccination with BNT162b2.

3.7 The EWG noted the sequencing of paragraphs 1 and 2 in Section 4.8 of the 'Information for UK healthcare Professionals document' could be reversed.

3.8 The EWG agreed that in Section 5.1 of the 'Information for UK healthcare Professionals document', the disease severity (mild), should be stated for cases of COVID-19 disease in both the vaccinated and placebo groups.

3.9 The EWG discussed whether the vaccine could be administered via subcutaneous administration (SC) for certain populations (those with bleeding disorders or those receiving anticoagulants) and noted the absence of data to support SC use. The EWG agreed administration should be intramuscular (IM) as per the clinical trial population. In general practice, it is routine to administer other vaccines e.g. flu vaccine via the IM route to patients

taking anti-coagulants but care is taken to apply pressure to the injection site for an adequate length of time. It was agreed this information and other relevant information, should be part of a training package for healthcare professionals. The EWG recommended that this information should be disseminated to the public. The EWG also noted existing guidance which advocates a risk-based approach but permits patients on oral anticoagulants to receive IM injections (Medicines Q and As, 'Can small volume intramuscular injections be given to patients taking oral anticoagulants?' 2018; NHS, SPS).

3.10 The EWG discussed the information presented in Sections 6.2 and 6.4 of the 'Information for UK healthcare Professionals document' with regard to the stability of the vaccine. The in-use shelf-life details are considered to be unclear, and it needs to be established whether the text implies that the vaccine is stable for 6 hours or 8 hours. The EWG noted this will be discussed further in the quality discussion.

3.11 The EWG considered information in the 'Information for UK healthcare Professionals document' with regard to immunocompromised patients and agreed a statement should be added that no data are available for use in immunocompromised and immunosuppressed groups. The EWG stressed the importance of the company designing robust post-authorisation studies to assess vaccine efficacy in immunocompromised and immunosuppressed patients.

3.12 The EWG agreed that all common adverse events are adequately reflected in the 'Information for UK Patients' document. The EWG heard the most frequent adverse events were usually mild or moderate and resolved within a few days post vaccination. The EWG heard the clinical assessment team are updating the 'Information for UK healthcare Professionals document' and 'Information for UK Patients' document in liaison with the company.

4. The EWG heard a summary on the quality aspects of BNT162b2

4.1 The EWG heard that the batches relevant for the UK for a potential Regulation 174 approval are developmental batches which are subject to change and two batches have been evaluated by MHRA. The company has offered three other developmental batches to be considered for use through Regulation 174. However, their suitability is uncertain at this point in time; one is manufactured at a facility MHRA is not familiar with, one contains lipid-associated particles which were partially characterised and an unidentified late migrating band was observed on capillary gel electrophoresis of the third batch which requires further investigation.

4.2 The EWG agreed that, making decisions on approval under Regulation 174 in a batch specific manner is the safest route available. However, this position may be adjusted to allow approval for multiple batches under Regulation 174 in the future, if adequate data are provided.

4.3 The EWG heard that concerns remain with the two original batches the MHRA are evaluating as the specifications for the drug substance and the drug product are too broad with regard to the upper and lower limits and therefore it is not currently feasible to compare these two batches to those given to subjects in clinical studies. Particular points of concern are mRNA integrity and particle size.

4.4 The EWG heard that the company proposed a 6-month shelf-life. For the two batches in question, only 2-week stability data (at both 2-8°C and -80°C ±10°C) for one batch were made available and issues such as mRNA degradation are emerging. In view of the limited stability data available, the designation of a shelf-life for the finished product would have to

be a judgement based on the stability data received by the MHRA and comparability to the clinical trial batch data.

4.5 The EWG noted it was important to have data on particular quality aspects such as length of RNA, 5'-capping of RNA, and success of lipid particle encapsulation to ensure efficacy is maintained.

4.6 The EWG noted the issue of public confidence if authorisation via Regulation 174 is permitted given the lack of qualification of the two batches under review. The EWG expressed the need to be aware of the potential cumulative effects, of multiple small risks / gaps in the data. The EWG noted that it is possible to perform immunological testing of some vaccinees to confirm surrogate measures of efficacy at the point of vaccine administration, and to request samples are provided to NIBSC for testing.

4.7 The EWG heard that data on shear stress have been requested but not yet received. The EWG noted MHRA are receiving data from the company on a daily basis.

4.8 The EWG enquired whether the MHRA are receiving the same data as provided by the company to the FDA. The EWG noted that it may be the case that the batches the FDA are evaluating are further along the development lifecycle than those allocated for the UK.

4.9 Discussions and conclusions

The Chair summarised the discussion and noted that the EWG considered the non-clinical aspects of the assessment could be favourable with mitigations in place in relation to women of childbearing age, pregnant women and lactating women. Similarly, the EWG considered the clinical aspects of the assessment could be favourable with the inclusion of the proposed changes to product information and post-authorisation commitments. However, the EWG considered critical issues remain in the quality aspects of the assessment and further consideration of the data are required.

4.10 The EWG agreed that a quality subgroup would convene with the MHRA assessment team on Saturday 28th November 10am to review the quality data further and to refer any quality conclusions to the Commission for consideration at the CHM meeting Monday 30th November.

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

5.1 None.

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

To be confirmed

The Meeting started at 14:50 and ended at 17:05.

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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.