COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 28th October 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
Professor H J Lachmann[1]
Professor P J Lehner
Dr S Misbah
Dr A Riordan
Professor C Robertson
Dr R Thorpe
Mrs M Wang

Invited Experts

Professor I J Douglas
[redacted]

Apologies

Sir M Jacobs
Professor P Shah
Professor T Solomon
Professor C Weir

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Supporting Specific Items

[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr M O'Kane - LD
[redacted] - LD
[redacted] - LD

MHRA Observers

[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC
[redacted] - MHRA-NIBSC

[redacted]
19th January 2021

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control

[1] Joined during item 3

1. Introduction and Announcement

1.1 The Chair reminded Members that the papers and proceedings are confidential and should not be disclosed.

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 declared interests and other relevant interests to date:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions. 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

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.

Professor Lachman – 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)

Invited Experts of the Covid-19 Vaccines Benefit Risk Expert Working Group declared the following interests:

Professor Douglas - Personal non-specific in Oxford University, lecturing fees in the last 12 months. Personal interest in GlaxoSmithKline – Shares, current holding Bayer – October 2019 fee for delivering investigator training related to Aflibercept. Non-personal in GlaxoSmithKline - current research grant
At the chair's discretion, Professor Douglas was permitted to remain for the discussion and to answer, but not ask, direct questions from the chair and other members.

[redacted] - Personal non-specific interest in AstraZeneca who provide [redacted] department at the London School of Hygiene and Tropical Medicine with an unrestricted research grant 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and Astra Zeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results**.** Other relevant interest as [redacted] is working on a statistical methodology paper and some of the co-authors are statisticians at Astra Zeneca in Cambridge. It's an academic paper on analysis of subgroups and neither I nor this work have anything to do with their business side (or any drugs at all).

The register of interests declared by participants had not been deemed to debar any other participation in line with the policy. No further interests were declared.

1.4 Apologies have been received from Sir Michael Jacobs, Professor Shah, Professor Solomon and Professor Weir for this meeting.

2. Minutes of the meeting held on Wednesday 14th October 2020

2.1 The minutes were approved as a true and accurate record of the proceedings, subject to the amendment of item 4.1.3.

3. BNT162b2 non-clinical assessment

3.1 The EWG considered the non-clinical Day 14 Assessment Report for the BioNTech Manufacturing GmbH COVID-19 mRNA vaccine BNT162 being developed for use in healthy subjects to prevent COVID-19 disease on exposure to SARS-CoV-2.

3.2 The EWG agreed that the pharmacokinetics posed no particular concerns. The EWG endorsed the points already raised by the assessor and agreed that further points of concern be raised for the company to address.

3.3 The EWG agreed that the company should discuss in detail the potential distribution of the test articles to sites other than the liver, in particular the draining lymph nodes, thymus and spleen, and the potential for binding to cell membranes in particular the neurones, and the potential consequences for safety.

3.4 The EWG agreed the company should either justify the use of a non-validated/non-qualified bioluminescence method to determine the biodistribution of a reporter

luciferase protein instead of detecting the actual BNT162b2 modRNA or provide the validation/qualification data. Any justification should include a discussion on the sensitivity of the method.

3.5 The EWG agreed the company should justify the use of the intravenous route of administration rather than the intramuscular (the clinical) route for the rat PK study and the utility of the study in terms of its clinical relevance should be discussed.

3.6 The EWG considered the pharmacology and agreed that overall, there were no major public health concerns. The EWG endorsed the concerns already raised by the assessor and agreed the company should be asked to answer some further points of concern.

3.7 The EWG agreed that the company should be asked to clarify the source of the antigen used in testing in animal and human assays. The nature of this antigen and if it is known to retain function should be described.

3.8 The EWG discussed study vr-vtr-10671 in rhesus monkeys and the data on IgG responses at day 14 and day 21 presented in figures on page 14 and 15. It was noted there are no similar data from testing at day 0 but results from T-cells at day 0 are presented. The EWG agreed to request company provide the baseline (day 0) data preceding these IgG responses, or if these are not available, to give an explanation for the absence of these data.

3.9 The EWG noted that no characterisation of antibody-dependent cell-mediated cytotoxicity (ADCC) activity of antibodies is presented but this may contribute to the mode of action of antibody induced by vaccination. The EWG agreed to request the company explain whether such testing is planned and if not to give a scientific rationale for the absence of such data.

3.10 The EWG discussed the programmed cell death protein-1 (PD-1) responses described in mice. The EWG agreed the company should be requested to discuss whether this indicates T-cell exhaustion and is evidence of a waning response, or if not, provide an interpretation of this response.

3.11 The EWG endorsed the points of concern raised by the assessor in relation to toxicology.

4. BNT162b2 clinical assessment

4.1 The EWG considered the SARS-Cov-2 vaccine rolling review critical clinical assessment report for the BioNTech Manufacturing GmbH COVID-19 mRNA vaccine BNT162 being developed for use in healthy subjects to prevent COVID-19 disease on exposure to SARS-CoV-2.

4.2 The EWG heard that this is the first cycle of clinical data in the rolling review process for this vaccine consisting of interim phase I immunogenicity and safety data together with data on the bioanalytical assay methods and validation. It was highlighted that the assessment is focused on the BNT162b2 vaccine candidate as it is this version that the company will be taking forward to Phase II & Phase III trials.

The EWG heard that the company anticipate that in the 3rd week November 2020 safety data for 15,000 subjects 2 months post dose 2 will be available, plus safety data on 30,000 subjects 1 month post the 2nd dose. Some 3-month post dose 2 data will also be available from the phase I studies. However, with the exception of a very small amount of 2m post dose 2 data from study BNT162-01, humoral immunogenicity data will only be available for up to 1m post dose 2. Six-month data is not expected until early next year. The EWG was asked to advise if this anticipated duration of humoral immunogenicity data would be sufficient to issue a licence with the condition to provide further data at a later date. The EWG agreed that in these circumstances this could be acceptable.

4.3 The EWG raised concerns about the differences in sensitivity obtained with the N-protein antibody assay in different laboratories (e.g., PHE, Roche and Pfizer) for convalescent samples taken > 14 days post polymerase chain reaction confirmation (albeit different samples) and recommended that efforts should be made to improve the sensitivity of the assay.

4.4 The EWG considered that characterisation of ADCC activity of antibodies may contribute to the understanding of the mode of action of antibody induced by vaccination. The EWG suggested to request the company clarify whether there is any data on ADCC activity available from study BNT162-01 or c4591001 and if not, whether there are any plans to investigate this.

4.5 The EWG discussed antibody binding and the observation that at 7 days post dose 2, subjects dosed with BNT162b2 showed complementary antibody binding (GMC) responses against the SARS-CoV-2 spike (S) protein S1 subunit and receptor binding domain (RBD) consistent with the functional antibody response (GMT). However, it was noted that this is not the case for the data 21 days after the 1st dose, with the binding IgG response much greater than that of the functional antibody. A similar pattern is seen with the interim data from study c4591001. The EWG recommended that the company should comment on this and clarify whether any data is available on the affinity of vaccine induced antibodies towards SARS-CoV-2 S protein S1 subunit and RBD.

4.6 The EWG commented that the strong T-cell response was promising, and that the intracellular cytokine staining data supported a predominantly Th1 response, consistent with the non-clinical data.

The EWG also noted that the immunogenicity responses were promising in the 65 to 85 years of age groups.

The EWG considered the statistical plan and agreed the company should be asked whether, in study c4591001, there are any elements in the study design to ensure that the randomisation is balanced within countries.

4.7 The EWG considered the need for a standard COVID-19 serum and agreed this would aid comparability between assays for different vaccines. The EWG heard that NIBSC timeline to establish such a serum is in December 2020 when there is an extraordinary meeting of the ECBS.

4.8 The EAG endorsed the points of concerns raised by the assessors in relation to the bioanalytical assays, immunogenicity, efficacy and safety.

5. Regulation of challenge agents in the UK – verbal update for information

5.1 The EWG heard an overview of the MHRA involvement in the regulation of human challenge studies in the UK.

5.2 The EWG heard that challenge agents can be administered to examine pathogenesis of a disease or to assess efficacy of a new vaccine or antiviral medicinal product. Such studies require a research ethics committee review and HRA have set up ethics committee just for challenge agents' studies. If the studies involve NHS sites HRA approval is also required and health and safety executive approval would also be required depending on how the agent is made and contained.

5.3 Only studies looking at efficacy of a medicinal product are considered a Clinical Trial Investigational Medicinal Product (CT IMP) which require MHRA approval. In these cases, the medicinal product would be considered a IMP and the challenge agent a non-IMP. In the assessment of the clinical trial both the IMP and non-IMP would be considered in terms of subject safety and would look at dosing, risk mitigations etc in line with standard clinical trial guidance for example first in human clinical trials.

5.4 In terms of public health if a company wanted to run a study which wasn't a clinical trial the MHRA could provide scientific advice as it would form part of a clinical trial at a later date. In this case MHRA would provide advice on the design of the study, safety monitoring, risk mitigations and manufacturing quality of challenge agent itself. The challenge agent would not receive a GMP certificate and the challenge study would not receive an CTA but would receive scientific advice from MHRA and committees.

6. Any Other Business

6.1 None.

7. Date and time of next meeting

7.1 The next meeting is scheduled to take place on **Tuesday 10th November 2020** at **2.30pm** to **5pm**.

Date and time of future meetings:

- **Tuesday 24th November (2.30pm - 5pm)**
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 13.32 and ended at 15:17.

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.

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