COMMISSION ON HUMAN MEDICINES (CHM)

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

Minutes of the meeting held on **Thursday 10th December 2020** at **14:30** 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[1]
Professor C Weir[2]

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

MHRA Observers

Ms R Arrundale - Policy
[redacted] - VRMM
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] (Accenture IT)
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

[redacted]

18th January 2021

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

[redacted]

[redacted]

[1] Joined during item 2

[2] Left 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 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 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 – 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 have been received from Professor Shah for this meeting.

1.6 MHRA gave the group training on how to access the links and manoeuvre around the dossiers.

2. AZD1222 Quality, Clinical & Batch Release Testing Review

2.1 The EWG heard an update on the quality, clinical and batch release testing aspects of AZD1222. The EWG heard that several different batches of vaccine have been produced for the clinical trials with different manufacturing scales and process. This difference in scale had led to a change in purification process which has given different vial particle concentration. The EWG agreed the company should use a single assay [redacted] The EWG discussed whether two different purification protocols could also be contributing an effect as well as the difference in dose. The EWG agreed the company should be asked whether the ratio of particles containing nucleic acid is known and the effect this may have on the final composition of the product.

2.2 The EWG agreed the company should be asked to provide data on the number of vials tested in this study and the standard deviation.

2.3 The EWG noted that the company is using [redacted] for Processes 1 and 2 and [redacted] for Process 3.

2.4 The EWG heard that the process has been refined since the issues were observed in May 2020, and so there is a question now whether the initial results are reproducible.

2.5 The EWG heard discussion on the issues around the preparation of the doses given to subjects in the AZD1222 trials with different dilutions and volumes administered according to SOPs changes with each batch. The EWG was explained the reason for a lower dose (LD) being administered after the change of manufacturer. The EWG heard that the company intend to submit the application for the SDSD dose regimen, i.e., two standard doses of $5x10^{10}$ viral particles. The EWG discussed whether to consider the study as intention to treat as proposed in the Company SAP (SDSD + LDSD with SDSD as a key subgroup), with the LDSD as an unplanned subgroup, or to disregard the low dose completely. The EWG agreed that the company could use LDSD as pilot data for another proper prospective study to confirm the efficacy finding.

2.6 The EWG noted that dosing regimens in the AZ trials had a lot of heterogeneity in the length of the dosing interval which may cause issues with the interpretation of the data. The EWG heard MHRA will receive an analysis by dosing interval shortly. The EWG heard the company have proposed a dosing window of 25-35 days and MHRA will check how it corresponds to that used in the clinical trial. The EWG considered that the dosing schedule may drive the immunogenicity more than the viral particle dose.

2.7 The EWG noted that in the Phase II part of the COV002 study for immunogenicity the interval between dose 1 and 2 is 28 days whereas in Phase III for efficacy in Study COV002 the median interval is 69 days for the SDSD group and in Study COV003 it is 6 weeks. The EWG considered that this may influence immunogenicity. The EWG noted that there was no immunogenicity data for the LDSD dose regimen in the Phase II part of COV002 and that the immunogenicity data for the LDLD dose regimen and SDSD dose regimen are very similar. The EWG considered that there is no intrinsic difference in immunogenicity between LD and SD. The EWG considered that there is no biological finding to support the high efficacy observed in the LDSD group.

The EWG noted the lower age in the LDSD group as it included only subjects 18 – 55 years old. The EWG heard the subgroup analyses (including by age) are expected 21 December 2020.

2.8 The EWG discussed an appropriate upper limit for the timing of the second dose. The EWG heard the aim would be to achieve the best protection in the shortest period of time. For example, if 50/60% protection is achieved at the first dose, then a longer interval (e.g. 6 weeks) would be appropriate for the second dose. Conversely if less protection was seen in the first few weeks, then the second dose could be at 4 weeks; however, clinical efficacy data would be required to support that.

2.9 The EWG heard that NIBSC have received all 3 batches and have tested 2 which met the defined specifications.

3. Update on Hypersensitivity reactions

3.1 The EWG heard an update on the hypersensitivity reactions observed in 3 individuals (2 reports of anaphylaxis and one suspected allergic reaction) following vaccination with the Pfizer/BioNTech vaccine.

3.2 The EWG heard that a warning has been included in Section 4.4 of the 'Information for Healthcare Professionals' for persons with history of immediate-onset anaphylaxis to a vaccine, medicine or food. The statement includes a warning that the second dose should not be given if there is anaphylactic reaction to the first dose. The EWG heard that a statement has also been included in Section 6.1 of the SmPC to inform that the vaccine contains polyethylene glycol/macrogol (PEG) as part of ALC-0159. The EWG heard that a statement has been included in Section 2 of the 'Information for Recipients' with regard to a history of serious allergic reaction to a previous vaccine, medicine or food. The EWG heard that a clarifying statement that the vaccine contains PEG as part of ALC-0159 has also been added to Section 6 of the 'Information for Recipients'.

3.3 The EWG heard that the broad warning regarding previous reactions to food, vaccine and medicines was added as a precaution. The EWG heard that it is not yet proven that PEG is the cause of the anaphylaxis and allergic reactions observed. The EWG noted that the advice will likely change over time as more evidence becomes available.

3.4 The EWG heard that the three patients who had reactions should be investigated, through NHS England, in allergy clinics such as the Cambridge clinic to determine whether PEG is the causal agent in this case.

3.5 The EWG heard that only healthcare professionals are currently administering the vaccine in appropriate settings with the appropriate equipment to manage anaphylaxis or other reactions.

3.6 The EWG heard that the contraindications (anaphylaxis) may be excluding approximately 5% of the population.

4. Future Steps / Any Other Business

4.1 The EWG heard MHRA-NIBSC have released two further batches of the Pfizer/BioNTech vaccine so Pfizer/BioNTech can now provide vaccine from 3 batches.

4.2 The EWG were asked whether people who have been vaccinated are allowed to donate blood/tissues or should this be deferred. Would the mRNA or lipid component be transmissible? Under normal circumstances individuals who have taken a non-live vaccine would not be deferred.

4.3 The EWG were informed that the company have provided non-clinical data from a second distribution study in the rat using radiolabelled LNP. Following a single IM dose of 50µg, over a 48-hour period, the distribution from the injection site was extensive with the majority of the tissues exhibiting low levels of radioactivity. Drug related radioactivity was detected in the brain, but only at very low levels, i.e. 0.02% of administered dose at 2 hours post-dose falling to 0.009% at 4 hours post-dose. The majority (18% of the administered dose) was located in the liver.

5. Date and time of next meeting

Monday 14th December 2020 at 12:30

The Meeting started at 14:31 and ended at 16:12.

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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.