COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 14th October 2020** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor D Goldblatt
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor C Robertson
Dr R Thorpe
Mrs M Wang
Professor C Weir

Invited Experts

[redacted]

Apologies

Professor I J Douglas (Invited Expert)
Professor N French
Ms S Hunneyball
Sir M Jacobs
Dr A Riordan
Professor P Shah
Professor T Solomon

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting Specific Items

[redacted] LD
Dr K Wydenbach - LD

MHRA Observers

[redacted] - LD
Dr S Branch – VRMM
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - LD
[redacted] - LD
Mr K McDonald - LD
[redacted] - LD
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD

[redacted]

Key

LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control

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. Sir Munir declared the following potential NPNS interests of an IMI project which will not start until 1 November 2020 in Pfizer, Janssen and Sanofi-Aventis

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

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.

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

[redacted] - Personal Specific interest, [redacted] is a member of a DSMB for clinical trials of a COVID-19 vaccine developed by CUREVAC, Germany - receive DSMB fees for this work. Personal Specific interest, [redacted] has declared for this meeting that [redacted] is now acting as a temporary consultant for GSK where he receives ad hoc consultant fees.

This conflict of interest (personal specific interest in **GSK**) was discussed prior to the meeting with internal management and government legal team. [redacted]

[redacted] was advised and requested to stand down as an invited expert from this EWG to address any potential perception of bias.
This is based on the overriding principles of the code on conflicts are impartiality and transparency, and the key question in relation to any potential conflict is whether it might give rise to a reasonable perception of bias. [redacted] understood the EWG's position and did not attend the meeting. [redacted] has stood down from this EWG.

[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 covering the period 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and AstraZeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results**.** Other relevant interest, [redacted] is working on a statistical methodology paper and some of the co-authors are statisticians at AstraZeneca in Cambridge. It's an academic paper on analysis of subgroups and is not related to the business side of the company or products.

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, Professors Douglas, French, [redacted] Solomon, Dr Riordan and Ms Hunneyball for this meeting.

2. Minutes of the meeting held on Tuesday 29th September 2020

2.1 The minutes were approved as a true and accurate record of the proceedings, subject to the amendment of item 5.3.

3. Update on Clinical Trials

3.1 AstraZeneca AZD1222

3.1.1 The EWG heard AZD1222 trials in the UK are continuing. The restart approvals had conditions which required further data to be submitted by the Sponsor: all conditions have subsequently been met. Additional information requested was not limited to the primary specific serious cases (SUSARs), but also other less serious suspected ADRs, including a discussion of neurological events related to the vector.

3.1.2 The data provided on the SUSAR / neurological ADR was first reviewed in a blinded manner, and then the review was repeated with case codes assigned. Findings were the same irrespective of blinding status: both concluded that no specific neurological or thrombotic / cardiovascular safety signal had arisen related to vaccine.

3.1.3 The current data demonstrated that adverse events are relatively evenly split between ChAdOx1 vaccinated group and the control group (Meningitis vaccine).

3.1.4 The AZD1222 trial in US remains on hold. in relation to SUSAR 2, MHRA have held no discussions with the FDA to date, but the sponsors have provided the MHRA with an identical full package of ADR data (line listings) as was given to FDA.

3.1.5 Some results for SUSAR 2 are outstanding and the Oxford trial investigators continue to follow this up.

3.1.6 The EWG noted the data on SUSAR 2 of suspected transverse myelitis, indicated a poor antibody response to SARS-CoV-2 spike protein, but it is yet to be clarified if the trial investigators have assessed the data in the context of the immune response to the vector. The EWG requested clinical data on the immune response to the vector (the anti-vector response). The EWG heard that the data is incomplete at present but is being collected in the form of anti-vector response at several time points as a tertiary endpoint. The CTU assessors will continue to follow this up.

3.2 Janssen trial

3.2.1 The EWG heard that Janssen have halted all trials of their adenovirus serotype 26-vector vaccine, noting the UK has not approved any Janssen vaccine trials. MHRA have conducted a rolling review of a phase 3 clinical trial application of their SARS-CoV-2 vaccine and issued grounds for nonacceptance, for which Janssen have confirmed receipt. The company are presently collecting data and further information on the ADR / illness which lead to the approved trials being halted and an update to the MHRA will be provided by Friday 16 October. The EWG heard that there are no UK participants in the trial, the majority of trial participants are recruited in the US, and to a lesser extent in Japan, whilst study centres in EU countries (Spain, The Netherlands) do not appear to be recruiting.

4. Rolling review of AZD1222

4.1.1 The EWG considered the non-clinical rolling review sequence 1 assessment report for the AZD1222 vaccine being developed for use in healthy subjects to prevent COVID-19 disease on exposure to SARS-CoV-2 which was presented to the EWB by the non-clinical assessor.

4.1.2 The EWG agreed the pharmacokinetics posed no concerns, the viral distribution was found to be mainly localised to the vaccination site (apart from some leak to the local lymph node) and viral distribution was not found systemically.

4.1.3 The EWG discussed the immunological responses seen in the four animal models. The EWG noted the monkey animal model is likely to mimic most closely the disease pathology seen in humans, and the physiological responses in the vaccine studies undertaken in this model are reasonably encouraging. The EWG noted that less virus was detectable in bronchoalveolar lavage gathered from vaccinated animals compared to controls, but there was little difference in terms of viral presence on nasal swabs between groups. The EWG considered that vaccinated animals may be protected from developing COVID-19 disease but could still host the virus and be a source of infection. The EWG noted this would likely have implications if the same paradigm occurs in the humans as community infection rates would only be expected

to be lessened in those directly vaccinated, with those vaccinated still able to spread infection.

4.1.4 The EWG noted the data indicating lung damage is reduced is positive and seems to be associated with a vaccine based neutralising antibody response, however a quantifiable degree of immune protection is not available from these animal studies.

4.1.5 There is not enough data available currently to rule out vaccine mediated antibody dependent enhancement of disease (vADE). The EWG noted discussions on the use of hamster models to explore the risk of vADE need to continue. The EWG agreed with the proposal to raise a potential serious risk to public health (PSRPH) to request the company submit a revised overview that considers further the risk of vaccine-associated disease enhancement following AZD1222.

4.1.6 The EWG discussed the evidence seen in the rhesus monkeys of T-cell activation and markers for T-cell exhaustion and whether this could be related to the high viral load given to the animals.

4.1.7 The EWG agreed to add a potential serious risk to public health (PSRPH) with regard to T-cell exhaustion, indicated by PD-1 expression. The company is requested to discuss whether this might cause a loss of vaccine response. The company should present its view as to whether there is a link to this and to the finding that the effect of vaccination, as seen on CT scans at day 5, had become negligible by day 12.

4.1.8 The EWG discussed the assays and whether they are harmonised, i.e. ELISA in humans and ELISA in animals. Inclusion of the macaque sera into the study would be helpful. The EWG also discussed interferon gamma assays and whether they are more specific for SARS-CoV-2 than T-cell proliferation assays. The issue of cross reactivity with seasonal corona viruses was raised in relation to T-cell assays and the following paper (a preprint) was referred to: Ogbe et al. T cell assays differentiate clinical and subclinical SARS-CoV-2 infections from cross-reactive antiviral response. Medrix, posted 29.09.2020.

4.1.9 A key feature of the SARS-Cov-2 virus is that a very high viral load is needed before signs of illness show. A vaccine is unlikely to address this.

4.1.10 The EWG discussed viral shedding and noted that, in humans, viral SAR-CoV-2 RNA including subgenomic RNA, has been detected in the upper respiratory tract in the absence of infectious virus. The EWG noted that it should be determined if the viral RNA detected is inactive residual RNA, or if it is infectious. However, the viral load given in the animal model was severe, via 4 different routes, and does not reflect the clinical nature of the challenge.
The EWG discussed how to interpret in humans, data gained in relation to vaccine constructs with other genes given to animals. There is a concern that may see reaction with an unintended target i.e. that antibody or cellular responses to the novel gene product may cross-react with an unintended target.

4.1.11 The EWG noted that it is very likely that a combination of humoral and cellular responses to the vaccine will be required in order to form appropriate protection from SARS-CoV-2.

4.1.12 The EWG noted that the numbers of animals involved in each study are small and also discussed implications of bias. The EWG agreed to include a point for clarification and to ask the company to comment on how the group sizes in the pharmacological studies in ferrets and rhesus monkeys were determined, including how statistical considerations played a part in these choices. This should include consideration of the magnitude of expected effect seen on challenge with SARS-CoV-2 virus.

4.1.13 The EWG agreed the immune response data is assuring but noted that animal studies do not necessarily give the clinical picture, which can only be derived from clinical studies. ADE is being explored but not concerning at present, based on limited data presently available.

4.1.14 The EWG noted they had previously discussed the approach to the toxicology data. it is not a full package, that is due next spring. The data is based on the ChAdOx1 vector already used in the malaria and MERS vaccines.

5. Any Other Business

5.1 The EWG noted the potential for mutations in the spike protein and the scope for effects on immunity. Additional expert opinions on this theme will be sought by the EWG. The EWG noted that the COG UK mass genome sequencing project is UK based and gives an important mode to investigate and map changes in serum antibody responses, provided the basis for identifying samples of interest is provided to COG UK. The EWG noted that COG UK will be invited to a future Vaccines BR EWG meeting and members of the EWG will be able to put questions to COG UK.

6. Date and time of next meeting

6.1 The next meeting is scheduled to take place on **Wednesday 28th October 2020** at **1.30pm** to **4pm**.

Date and time of future meetings:

- **Tuesday 10th November (2.30pm - 5pm)**
- **Tuesday 24th November (2.30pm - 5pm)**
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 10:31 and ended at 11:41.

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.