COMMISSION ON HUMAN MEDICINES (CHM) COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on Friday 21st May 2021 at 14:30 via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)

Professor J Breuer

Professor G Dougan¹

Mr VI G Fenton-May

Professor N French

Professor D Goldblatt

Ms S Hunneyball

Professor K Hyrich¹

Sir M Jacobs²

Professor H J Lachmann

Mr R Lowe

Dr S Misbah

Professor Y Perrie

Professor S Price

Dr A Riordan

Professor K M G Taylor

Dr R Thorpe

Professor M Turner

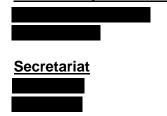
Dr S Walsh

Professor C Weir

Apologies

Professor P J Lehner Professor C Robertson Professor T Solomon Mrs M Wang

Observers (left after item 3)



<u>Professional Staff of MHRA Present</u>

Principal Assessors

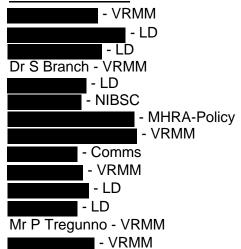
Dr J Bonnerjea - LD



Presenters supporting specific items

- LD - VRMM - VRMM - VRMM - LD

MHRA Observers





3rd August 2021

<u>Key</u>

LD = Licensing Division

VRMM = Vigilance & Risk Management of Medicines

NIBSC = National Institute for Biological Standards & Control

Comms = MHRA Communications

¹ Left during item 5

² Joined during item 3

1. Introduction and Announcement

1.1 The Chair reminded Members and observers 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 Participants declared interests and other relevant interests for this meeting listed at **Annex** II to the minutes.
- **1.4** Apologies were received from Professors Lehner, Robertson, Solomon and Mrs Wang for this meeting.
- **1.5** The Chair welcomed the following observers:



2. Communications on COVID-19 vaccine safety

- 2.1 The EWG discussed a paper which presented options for analyses of safety data related to the occurrence of thrombotic events with concurrent thrombocytopenia that could be considered for routine publication within the `Coronavirus vaccine weekly summary of Yellow Card reporting'.
- The EWG supported transparency with regards to the publication of data on this risk but advised that the data needs to be carefully presented to ensure its limitations are clear and that estimates based on small numbers which may be unstable and/or inadvertently disclose confidential patient information should be avoided.
- 2.3 The EWG supported the publication of age-stratified incidence reporting rates for thrombosis with concurrent thrombocytopenia following both doses of the COVID-19 AstraZeneca vaccine alongside an accessible and clear description of the benefits and risks of vaccination.

3. Update on the Safety Data for the Moderna COVID-19 vaccine

3.1 The EWG was presented with the first safety update for the Moderna COVID-19 vaccine, which covered the first month following deployment in the UK, with a data lock point of 12th

May 2021. The EWG was informed that the ADRs reported were broadly in line with the known safety profile for the vaccine and that had been seen in clinical trials. The EWG heard a signal of dizziness has been identified for the Moderna COVID-19 vaccine, which included reports of dizziness alongside psychogenic, reactogenic and vestibular events. The EWG were informed that the Marketing Authorisation Holder (MAH) had been requested to review the signal of dizziness with a particular interest in cases reporting vestibular events such as tinnitus. The meeting supported the continuous review of dizziness reports. An update to the EWG will be provided following the MAH review.

- The EWG were informed that a large proportion of the Yellow Cards reported for the Moderna vaccine were related to delayed injection site reactions. These reactions include a large, raised, itchy red rash around the injection site around 7 to 8 days after vaccination. The meeting was informed that the MAH had updated their Company Core Data Sheet (CCDS) to include these delayed injection site reactions and were planning to update the product information in due course. The meeting supported the proposed update to the product information to highlight these delayed reactions to patients.
- The EWG concluded that based on the data presented, the safety profile for COVID-19 vaccine Moderna was broadly in line with the expected safety profile from clinical trials. The EWG supported the proposed actions on the delayed injection site reactions and dizziness signals.

4. Covid-19 mRNA vaccine BNT162b2

- 4.1 The EWG heard that immunobridging of neutralising antibody levels between adolescents aged 12-15 years and young adults aged 16-25 years has been established and that the neutralising antibody levels seen in adolescents actually exceeded those in young adults.
- 4.2 The EWG noted that these immunobridging results are supported by a very high level of short-term efficacy data in adolescents against symptomatic disease after 2 doses of the vaccine.
- 4.3 The EWG heard that the safety data in adolescents was generally comparable with that seen in young adults, with the majority of adverse events being mild to moderate and relating to reactogenicity. Additionally, no new adverse events are identified in the trial. The EWG noted that 3 serious adverse events of depression were reported in the adolescent group compared with 2 non-serious reports in the placebo group. All 3 subjects had a significant past medical history that included depression, but none were considered related to the vaccine and 2 of the 3 cases resolved after 5 days. The EWG agreed that currently there was no basis to list depression as a safety concern in the RMP. However, this will be kept under review in the post authorisation period, through the monthly summary safety reports submitted by the company.
- The EWG noted that overall, when compared to adults 16-55 years of age, there is an increase in reactogenicity seen in adolescents. However, it was agreed that this is not unexpected as the same trend was seen previously in subjects 16-55 years compared with those aged > 55 years of age. This trend is already reflected in the GB SmPC for the conditional marketing authorisation and this wording will be aligned in the Regulation 174 product information.
- 4.5 The EWG were made aware of an open letter that has been received by the MHRA, signed by over 40 UK doctors, raising their concerns about covid-19 vaccination in children. Other media coverage was highlighted on the ethics of vaccinating children and adolescents that have a low risk of severe COVID-19 whilst the majority of the adult population worldwide is

not yet vaccinated. The EWG concluded that while the latter is an important moral and ethical question it is not one for the EWG to address as the licensing remit of the MHRA focuses on the assessment of the quality, safety, and efficacy of medicinal products.

- The EWG discussed the adequacy of the efficacy and safety follow-up duration available in subjects aged 12-15 years (median > 2months). It was noted that this duration is the same as what was previously agreed for subjects aged 16 years and over. The EWG agreed with the Paediatric Medicines EAG that it seems reasonable to be on the same line for adolescents, particularly given the significant post-marketing safety data now available for this vaccine. The EWG noted that it is anticipated for younger children under 12 years of age, longer term safety data would be requested before any approval.
- 4.7 The EWG were made aware that no notable changes were proposed by the company to the risk management plan in terms of the safety concerns, pharmacovigilance plan or risk minimisation measures. The EWG agreed that based on the available safety data, no additional safety concerns specific to the adolescents aged 12-15 years are required at this time.
- 4.8 The EWG noted that the list of adverse events of special interest (AESIs) for COVID-19 vaccine BNT162b2 already includes events of relevance to the adolescent age group, including narcolepsy, chronic/post viral fatigue syndrome, myalgic encephalomyelitis, post orthostatic tachycardia syndrome and paediatric inflammatory multisystem syndrome. The EWG noted that these events will be subject to observed-expected analyses and that age-appropriate background rates should be considered by the company. The EWG agreed with the proposed questions to the company, including requesting a discussion on how safety data in the adolescent population could be collected in existing PASS studies, and the inclusion of a separate analysis of safety data in the adolescent population in the monthly summary safety reports.
- 4.9 The EWG noted the clinical trial data continues to be blinded to participants and clinical trial investigators except if participants are offered vaccination under emergency use authorisation, but the data have been unblinded to the independent scientists that undertook the statistical analysis.
- 4.10 The EWG noted immunogenicity and safety data in the 12-15 year olds provides a good level of reassurance. The efficacy data is also supportive of a positive recommendation albeit that the data is limited in this age group.
- **4.11** The EWG noted vaccination of 12-15-year olds could be an important means by which to limit the evolution of SARS-CoV-2 through controlling circulation of the virus.
- 4.12 The EWG noted that careful consideration may need to be paid to the natural background mental and behavioural health of 12-15-year-olds when assessing vaccine surveillance safety data, as this age group are likely to have been particularly affected by the pandemic.
- **4.13** The EWG agreed that six months follow-up data in 12-15 years should be added as a condition.
- 4.14 The EWG agreed with the conclusions of the Paediatric Medicines EAG. The EWG endorsed the clinical assessor's recommendation, that the Regulation 174 approval can be amended to lower the indication age to 12 years and above.

- 5. A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents (aged 6-17) COV006
- The EWG heard the proposal to continue dosing in the Oxford paediatric trial and to administer booster/second doses is supported by the CTU. Use of the AstraZeneca COVID-19 (AZD1222) vaccine in UK national deployment has been restricted by the Joint Committee on Vaccination and Immunisation (JCVI) following reports of extremely rare adverse events of concurrent thrombosis and thrombocytopenia following vaccination with the first dose of AZD1222. However, such a risk has not yet been convincingly demonstrated for second doses.
- The risk of thrombosis with concurrent thrombocytopaenia has not been demonstrated for any doses in children and is therefore not known. A total of 261 children aged 6-17 years have received the prime dose with no complications and 74 children aged 12-17 years have been given their booster doses on Day (D) 28 also with no complications. The EWG heard, the MHRA-CTU has reviewed the safety profile of the 74 children in the older age group (12-17 years), where the prime and booster doses were administered on D28 with no safety concerns identified; and together with consideration of the updated benefit risk assessment provided by the Sponsor, the proposal to administer a booster dose to the remaining 76 older children and the remaining 111 younger children (aged 6-11years) in this trial is supported.
- 5.3 The EWG also heard that appropriate additional safety blood tests have been introduced. at D2 and D7 for a subset of 6-11 year olds (20 participants at each timepoint post boost). These include full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT) and C-Reactive protein (CRP), with clotting studies. Trial participants will also be fully informed of the potential risks (with the ability to withdraw should they choose). Administering booster doses to the children in this trial will provide data to demonstrate efficacy which could be crucial for having a COVID-19 vaccine for specific groups within the paediatric population in the future and for any future variant vaccine. Immunogenicity data from prime (single-dose) dosing in the COV006 cohort is pending. However adult studies show that a single dose provides 76% protection against symptomatic infection, which persists over at least a 12-week period rising to >82% after a second and providing prolonged protection. If similar results can be extrapolated to the paediatric population, a second dose is required for prolonged efficacy and if the booster doses are not given trial participants will complete the trial having not been fully vaccinated, i.e. not fully covered against COVID-19, which has ethical considerations.
- The EWG heard on 19th May the Paediatric Medicines EAG broadly agreed that the trial could proceed with administering booster doses. And, that overall, the risk mitigation in place was considered appropriate. However, there was discussion around the updated patient information and the advice that those with headaches persisting more than 4 days after vaccination should seek medical assessment. Experts noted that 4 day headaches are rarer in children compared to adults and felt this should be reconsidered and trial participants asked to seek advice earlier.
- 5.5 The EWG was asked to provide advice to the Clinical Trails Unit (CTU) regarding dosing of second doses to paediatric subjects within an ongoing clinical trial using the AZD1222, and to discuss the 4 day duration of headache in the patient advice.
- 5.6 The EWG noted the additional safety blood tests, and proposed D-Dimer to also be included. A member noted that the trial should be allowed to proceed on the basis of a) the

additional blood tests to be included b) that no convincing cases of thrombosis with concurrent thrombocytopenia have occurred at second dose, and c) that participants and parents / guardians of participants will be reapproached for consent with much clearer information. The member also noted that it is also important to complete the study in order to gain as much data / information as possible.

- The EWG noted an argument in favour of providing a booster dose, and the possibility of enhanced protection which could be afforded to the participants. This argument was noted to carry two substantial caveats: the majority of the paediatric population has not been vaccinated because the risk of moderate / severe disease is extremely low in these young age groups, and secondly the purpose of a clinical trial is not to provide clinical care to the participants. In an interconnected point the EWG also referred to good clinical practice (GCP) and the stipulation to protect trial participants from risk supersedes the need for science to understand the article being tested. In this trial there is a very small but potentially very serious risk of thrombosis with concurrent thrombocytopenia associated with the vaccine at first dose, which could theoretically occur with the second dose in children.
- 5.8 The EWG noted if the trial was to proceed, the interval between doses will be approximately 3.5 months for those children awaiting their second dose and this would make data comparison e.g. immune bridging of data difficult to interpret because the data collected from adults is of a shorter interval.
- The EWG noted that recent surveillance data in adults has identified cases of thrombosis with concurrent thrombocytopenia after the second dose. However, the rate is far less than that reported following first dose and it is not clear whether the rate is any higher than the expected background rate.
- Thrombotic events in adults appear to be immune mediated, as such, it is plausible that the incidence could also be similar in children, who are capable of powerful immune responses. However, the data to help understand the aetiology or mechanism of this SAE is limited in adults and non-existent in children. Therefore, predictions of incidence of the risk of thrombosis with concurrent thrombocytopenia upon vaccination in children will be unreliable at this stage. The member disclosed a conflict of interest, i.e. being the father of two children in the age ranges that are subject of the trial.
- The EWG noted that second doses of AZD1222 are being given to people in the general UK population (including those under 40 years) who have had their first dose of the same vaccine.
- The EWG noted that should the trial continue, the data gathered could be relevant / valuable to future vaccine campaigns in other nations. Notable limitations were also discussed: children in developing countries often respond differently to vaccination, surveillance systems to identify rare adverse events are often not available in many developing countries, and campaigns in these countries in many cases are only just beginning to vaccinate older at-risk populations.
- The EWG further discussed the pros and cons of continuing the trial through to completion. The group arrived at the below list of questions to be sent to the trial Sponsor in expectation that the answers may help to better inform the Commission on Human Medicines (CHM).
 - 1. The original purpose of the trial has been questioned. The original study was presumably set up to study immunogenicity of ChadOx1 in younger age groups to aid the extension of any approval to younger age groups. How will D112 booster data be used to aid in the evaluation of ChadOx1 in young children in

the UK, for example to support national rollout or to support vaccination of specific vulnerable groups?

- If not relevant to UK children (given the fact it is unlikely the AZ vaccine will be rolled out to children in the UK) how could data from the trial be used to support / inform dosing in children in other countries e.g. under developed countries.
- 3. How will the fact that the data generated from continuation of the trial which may be of little value to children in the UK be shared with trial participants / parents in patient facing documents?
- 4. D-dimers should be added to the safety bloods.
- 5. Blood testing measures are possibly falsely reassuring given that once abnormalities are detected there is often no successful intervention (seen in the VITT first dose patients). Would this be explained to families?
- 6. The direct benefit of the trial to the individual or generally is quite remote. Individual benefit of vaccination with this vaccine for younger individuals when balanced against risk is low and it is unlikely to be used in the UK in this population. If used in the rest of the world, the patient population will be different from the population in this trial.
- 7. Does the immunogenicity data suggest that a second dose is actually needed for children?
- 8. How will the data generated by boosting the remaining children be of use (since the AZ vaccine is unlikely to be given to children in resource rich settings and not a priority in resource poor settings)?
- In post meeting email correspondence, a small number of additional questions were also suggested by members of the EWG, these are listed below for ease of reference:
 - 1. Will parents be asked to re-consent for the booster dose as the balance of risk/ benefit has changed since their original consent was taken?
 - 2. Even if the issues can be addressed by a very detailed consent process, should this population be asked to give consent? It is already a difficult population for consent purposes, i.e. parents of nearly Gillick competent children and/or immature but Gillick competent children. They will be subject to the pressure of being asked to continue in a trial for a life-saving vaccination by a world leading institution in face of a global pandemic. Trial participants will be under pressure to consent and such pressure is increased given that if they say no, other subjects cannot be obtained, and the trial cannot proceed. Individual choice is usually favoured however in such circumstances it is questionable whether consent can be ethically attempted.
 - 3. The paper states that there "There have been no clearly identified safety concerns identified for thrombosis/thrombocytopenia associated with the second dose of the AstraZeneca (AZD1222) vaccine." This statement does not refer to the very rapid increase in understanding, and possible future position; in that information is building slowly but as it is a rare disease and more first doses given than second the picture may not be complete. The risk, albeit slight, is confirmed by introduction

of blood testing measures in the study itself. Would this slight risk be communicated to participants?

4. 'Thrombosis' should be added as a stopping criterion.

6. Any Other Business

None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 24**th **May** at **5.15pm**.

The next scheduled meeting is to take place on Tuesday 25th May at 12.00pm.

The Meeting today started at 14:31 and ended at 16:05.

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.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - <u>NPNS</u> 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 on 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 references all sources of information used.

Professor Hyrich – <u>NPNS</u> - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. <u>NPNS</u> Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. <u>NPNS</u> 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.

Professor 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).

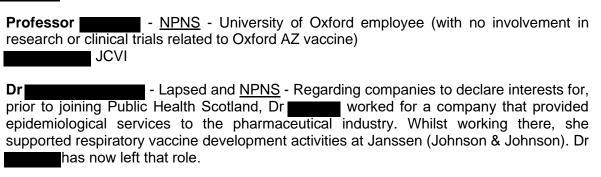
Professor Price - <u>NPNS</u> in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

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).

Mrs Wang – <u>Other relevant interests</u> arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers



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