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

Minutes of the meeting held on **Tuesday 13th December 2022** at **09:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Ms S Hunneyball
Professor H J Lachmann
Mr R Lowe
Dr S Misbah
Professor S Price
Dr A Riordan[1]
Professor C Robertson[1]
Professor K M G Taylor [2]
Dr R Thorpe
Professor S Walsh[2]
Mrs M Wang
Professor C Weir

Apologies

Professor N French
Professor D Goldblatt
Professor K Hyrich
Professor P J Lehner
Professor Y Perrie
Professor M Turner

Invited Experts

[redacted][3]
[redacted]
[redacted][4]
[redacted][4]

Observers

[redacted]
Professor W S Lim
[redacted]
[redacted]

Secretariat

[redacted]
[redacted]

Professional Staff of MHRA Present

Principal Assessors

[redacted] - HQA
[redacted] - S&S

Presenters supporting specific items[5]

[redacted] - HQA
[redacted] - HQA
[redacted] - S&S
Dr S Hopper – HQA

MHRA Observers

[redacted] - S&S
[redacted] - HQA
[redacted] s - S&S
[redacted] - S&S
[redacted] - HQA
[redacted] - HQA
[redacted] - HQA
[redacted] - S&S
[redacted] - Comms

Government Legal Team

[redacted]

[redacted]

16th February 2023

[1] joined during item 4
[2] left during item 3
[3] presented item 3
[4] presented item 2
[5] presented specific items

Key

HQA = Health Quality & Access Group
S&S = Safety & Surveillance Group

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts 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 French, Goldblatt, Hyrich, Lehner, Perrie and Turner for this meeting.

1.5 The Chair welcomed the following presenters as invited experts to the meeting:

Item 2: Short mRNAs and adverse events

[redacted] Cambridge University
[redacted] Cambridge University

Item 3: Vaccination Errors

[redacted] NHSE
[redacted] NHSE (observer)
[redacted] PHW
[redacted] NI (observer)

1.6 The Chair welcomed the following observers to the meeting:

[redacted]
JCVI

[redacted]
[redacted] Public Health Scotland

Professor Wei Shen Lim
Chair of JCVI

2. Short mRNAs and possible link to adverse events

2.1 The EWG heard a presentation from the Medical Research Council (MRC) Toxicology Unit at the University of Cambridge on '*On and Off target toxicities associated with RNA-based therapeutics: m in vitro-transcribed (mIVT) mRNAs*'. The researchers reported their initial study findings that [redacted] used in Moderna and Pfizer COVID-19 vaccines led to aberrant translation and generation of an off-target peptide product. T cell responses could be detected against these off-target products in multiply immunised mice and people at an approximately 20-fold lower level than the on-target response. The researchers concluded that larger studies sampling affected tissue would be required to determine if their findings of a frame-shift effect had any role in mRNA COVID-19 vaccine-associated toxicity. The researchers also considered that these findings may be particularly interesting given the other potential applications of this technology in addition to COVID-19 vaccines.

2.2 The EWG discussed these findings with the researchers and their plans to study the issue further. The researchers informed the EWG that they were beginning work to look at larger datasets and that while they were unsure if they would be able to obtain sufficient samples for studying patients who experienced possible toxicity post-vaccination, they thought they would be able to quantify how frequent the off-target responses were in various immunised populations (around 7% in their current data).The possibility of a potential role of an off-target effect in the cases of very rare myocarditis in association with mRNA COVID-19 vaccines was also discussed; however it was noted that myocarditis had now been identified as a risk for the non-mRNA Novavax COVID-19 vaccine which may suggest that a frame shift effect may be unlikely to be responsible for carditis although further investigations were required (for example, studies to examine T cell responses in tissue related to a toxic event).

2.3 Overall, the EWG considered that it was important to understand the clinical consequences of the researchers' findings and supported the further work the researchers were undertaking to investigate this further.

3. Vaccination errors with the COVID-19 vaccines

3.1 At the prior request of the EWG, two invited experts from NHS England and Public Health Wales presented data on vaccination errors in those countries with the COVID-19 vaccines. Data on vaccination errors in Scotland and Northern Ireland will be presented to the EWG by Public Health staff from those devolved administrations at a future date.

3.2 In the presentation on COVID-19 vaccination errors in England, the EWG was informed that a median of 8 incidents were reported to the National Reporting and Learning System for every 100,000 COVID-19 vaccinations administered. This figure was highest in patients aged 18 to 35 years of age and lowest in those aged 56 to 75 years of age.

3.3 The main type of error reported with the COVID-19 vaccines was 'right vaccine'-type errors, where an incorrect vaccine or an incorrect dose was given. Examples of recent errors involving incorrect vaccine type administered included Spikevax being given to under 18-year-olds, Comirnaty 30mcg given to under 12-year-olds and the wrong type of flu vaccine given for the patient's age (when co-administered with a COVID-19 vaccine). The main example of a recent error involving incorrect vaccine dose administered was underdosing with the Moderna Original/Omicron BA.1 bivalent vaccine booster, partly due to electronic prompts in the Point of Care system causing confusion among vaccinators and the fact that the Moderna monovalent booster was given at half the dose of the primary series.

3.4 The EWG was informed that incident report analysis is subject to some quantitative inaccuracies due to lag times in reporting. The reporter's perception of the seriousness of an incident can vary with time and circumstances. As more vaccines with different handling requirements are approved, the risk of errors occurring increases. Most vaccination errors involve human factors, but some can be anticipated from poor vaccine design. The speed of delivery of new products makes it difficult for these design issues to be fully mitigated.

3.5 In the presentation on COVID-19 vaccination errors in Wales, the EWG was informed that, in Wales, the Health Boards record incidents locally and there is no national recording of vaccine administration errors.

3.6 In considering use of COVID-19 vaccines outside of the licence in Wales, an analysis of use of bivalent vaccines in patients under 18 years of age was presented. A small number of cases of off-label use in patients younger than the approved age groups was noted for both Comirnaty and Spikevax. There were also cases of the bivalent vaccines being given for primary immunization outside of the licence which only permits use of these vaccines as boosters. An investigation is ongoing to understand the data quality and other factors which may have caused off-label use of the bivalent vaccines in children.

3.7 Cases of underdosing with the Moderna Original/Omicron BA.1 bivalent vaccine booster were described, arising in 2 main incidents in September 2022 and reported to Welsh Government Chief Medical Officers under a 'no surprises' approach.

3.8 The EWG noted that, in the context of the huge numbers of COVID-19 vaccine doses given, some vaccination errors would be expected, but it remains important to understand their causes and mitigation. The EWG acknowledged the underreporting of incidents and the authorities' approach that errors occurring in specific locations are likely to be occurring more widely across the service and should be addressed with country-wide solutions. The EWG noted the critical importance of providing robust training to those involved in delivering the vaccines and of providing updated training whenever a new COVID-19 vaccine product is approved, or an existing marketing authorisation is extended. The EWG noted that the use of different vial cap colours to differentiate strengths or age categories within vaccine brands, currently utilized by some manufacturers, is limited as a means of mitigation and should be used in conjunction with written information on the labels to minimize incorrect vaccine type or dose errors. The EWG encouraged the MHRA to work with international regulatory authorities, where possible, to achieve standardization of the physical characteristics of the products to reduce errors.

4. Spikevax 0.1 mg/mL dispersion for injection (Elasomeran) PLGB 53720/0005 – 0008

4.1 The EWG noted Tabled Paper I.

4.2 This variation application via the European Commission Decision Reliance Procedure (ECDRP) is to extend the use of Spikevax to the paediatric population aged 6 months to 5 years as a primary series of two [redacted] doses 28 days apart.

4.3 The EWG heard a summary of the clinical data from study mRNA-1273-P204, the pivotal immunogenicity and safety study in support of the application. For the primary immunogenicity endpoint of geometric mean concentration at day 57, the results demonstrated that neutralising antibody levels against the ancestral strain (D614G) were non-inferior to those of a pre-specified cohort of young adults from study mRNA-1273-P301. The EWG considered that the immunogenicity data were convincing.

4.4 The results of descriptive vaccine efficacy analysis in 5476 participants from 14 days post-Dose 2 were 36.8% (95% CI: 12.5, 54.0) for children aged 2 to 5 years and 50.6% (95% CI: 21.4, 68.6) for children aged 6 to 23 months. No severe cases were reported. The EWG noted that these estimates were based on relatively small numbers and were sensitive to the case definition.

4.5 The solicited adverse reactions in children less than 3 years of age were adapted to include irritability/crying, sleepiness and loss of appetite. The reactogenicity profile in children aged 6 months to 5 years was in line with that observed in older individuals. There were no cases of myocarditis/pericarditis and no new safety concerns were raised.

4.6 The EWG heard a summary of post-approval data from the US in children aged 6 months to 5 years based on over 440,000 doses administered. The data were consistent with the clinical trial data. There were no reports of myocarditis/pericarditis or unexpected safety findings. The EWG were reassured by the safety findings. However, the EWG noted that medication error was common in the US and was likely to occur in the UK due to the different COVID-19 vaccine formulations, doses, regimens and dosing volumes.

4.7 The EWG heard that the risk management plan (RMP) was updated in line with the variation. The list of safety concerns was unchanged. The EWG provided additional product information comments for MHRA consideration.

4.8 The EWG considered that children aged 6 months to 5 years who were vulnerable (such as those with neuro-disability) were most likely to benefit from Spikevax.

4.9 The EWG considered that vaccine effectiveness in children aged 6 months to 5 years should translate to a reduction in the incidences of severe COVID-19, MIS-C and long COVID, and these data should be provided post-approval to confirm the risk-benefit.

4.10 In conclusion, the EWG advised that the variation could be approvable provided that the MAH first discussed the feasibility of including a composite endpoint of severe COVID-19, MIS-C or long COVID in the ongoing post-approval effectiveness study.

5. VidPrevtyn Beta PLGB 46602/0028 Sanofi Pasteur

5.1 VidPrevtyn Beta is an adjuvanted protein-based vaccine containing a recombinant spike protein of the SARS-CoV-2 B.1.351 strain. On 10 November 2022, it was authorised by the EC for booster immunisation to prevent COVID-19 in adults having received an mRNA or an adenoviral-vector vaccine as primary series. An application has been submitted to the MHRA through the European reliance procedure.

5.2 The EWG was presented with the immunogenicity data that supported this booster indication based on a comparison with Comirnaty (prototype against the ancestral strain), i.e. using an immunobridging approach, which is considered acceptable. The EWG agreed that the product could be granted a full GB marketing authorisation with the same recommendations as those expressed by EMA/CHMP.

5.3 The EWG also considered the question raised to them to advise on potential use of the vaccine for primary immunisation purposes. Based on the data available to them from the booster dose, its safety profile, the nonclinical and in vitro data, the biological plausibility as well as the immunogenicity, the EWG considered that use of VidPrevtyn Beta for primary immunisation may be an acceptable clinical option. This opinion is aligned with European Commission decision and advice from the Emergency Task Force on the use of the EMA approved bivalent original/Omicron BA.4-5 mRNA vaccines for primary series.

5.4 The EWG were presented with a summary of the Risk Management Plan (RMP) that was submitted as part of this ECDRP application for VidPrevtyn. The safety specification, pharmacovigilance plan and risk minimisation measures were presented to the EWG for their consideration. The EWG discussed how a GB-specific annex to the EU RMP would be required in order to facilitate additional GB monitoring requirements in line with other COVID-19 vaccines. These are to be handled by the Applicant as GB-specific post-authorisation measures.

5.5 The EWG were made aware of the inclusion of the 15-minute observation time within the Summary of Product Characteristics for VidPrevtyn. As a formal deployment schedule has not been formalised within the UK, the EWG discussed that the 15-minute wait time for patients receiving a routine booster with no past history of hypersensitivity should be waived in line with previously endorsed discussion with regards to the mRNA vaccines; however for patients with previous hypersensitivity, observation time should remain as a recommendation in line with the Green Book. When a formal deployment plan is formulated, this recommendation may need to be re-addressed.

5.6 The EWG endorsed the conclusion that the RMP is considered acceptable in line with CHMP opinion, and that the additional requirements to the RMP can be handled as GB-specific post-authorisation measures.

6. Any Other Business

6.1 None.

7. Date and time of next meeting

The next meeting is to be arranged.

The Meeting today started at 09:31 and ended at 12:09.

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.

Annex II

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

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 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).

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 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 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).

Mrs Wang - Other relevant interests 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

[redacted]**r** - NPS – was part of an expert working group [redacted] with [redacted] conducting the initiative on behalf of [redacted] to discuss strategies to improve 'vacceptance'. [redacted] has not received any form of payment or other remuneration as described above but a paper is expected to be published.

[redacted] - NPNS - arises from the institution [redacted] where [redacted] works has received unrestricted investigator-initiated research funding from [redacted] for an unrelated prospective population-based cohort study [redacted]