COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 22nd December 2020** at **11:30** 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[1]
Professor P Shah
Professor T Solomon[2]
Dr R Thorpe
Mrs M Wang
Professor C Weir

Members of the CTBV EAG

Professor B K Park
Professor M Turner

Members of the CPS EAG

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston[3] (Chair of CHM)

Invited Experts supporting item 2

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted]
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
Ms R Arrundale - Policy
Dr S Atkinson – Dir
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
Ms T Moore - IE&S
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - LD
[redacted] - MHRA-NIBSC
Dr J Raine - MHRA CEO
[redacted] - LD

Observers for specific items

[redacted] – Public Health England
[redacted] – Public Health Scotland

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

Representative from University of Oxford

[redacted]

Secretariat

[redacted]

[1] Joined during item 3
[2] Joined left after item 5
[3] Joined 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
MHRA CEO = Chief Executive
Dir = Director of Operational Transformation
IE&S = Inspection, Enforcement & Standards
EAG = Expert Advisory Group

[redacted]

18th January 2021

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 – Other relevant 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.

Invited Experts for this meeting

[redacted] – NPNS - in AstraZeneca and a PNS interest in AstraZeneca and was permitted to participate in the meeting to answer direct questions from the Chair only

[redacted] - NPNS interest in Imperial College London

Observer for this meeting

[redacted] - NPNS interest in Pfizer

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)

Invited Experts who participated for the anaphylaxis item 2:

[redacted] MA(Hons) Cantab., MSc, BS, DCH, FRCPCH, FHEAm Dip. Allergy Consultant Paediatric Allergist, Guy's and St Thomas' Hospitals, London; Reader in Paediatric Allergy, King's College London

[redacted] MB BS, MD, FRCP Consultant in Allergy and Asthma, Cambridge University Hospitals NHS Foundation Trust

[redacted] MBBS, MD, MRCP(UK), MBA, FRCP, FRCPath Consultant Immunologist, Sheffield Teaching Hospitals; Chair of the Speciality Advisory Committee for Immunology, Joint Royal Colleges of physicians Training Board

[redacted] Honorary Consultant in Paediatric Allergy and Immunology, London; MRC Clinician Scientist in Paediatric Allergy and Immunology, Imperial College London

The invited experts left after item 2.

Representatives of the Public Health Bodies attending as observers:

[redacted] – Public Health England

[redacted] – Public Health Scotland

The observers left after item 3.

1.5 At 13:14, the Chair welcomed

[redacted] FRCPCH PhD FMedSci
Professor of Paediatric Infection and Immunity, [redacted], Department of Paediatrics, [redacted], [redacted] University of Oxford

[redacted]

Who gave a slide presentation on ChAdOx1 nCoV-19. The representatives answered questions from the Group, then left the meeting.

2. Update on BNT162b2 risk of anaphylaxis

2.1 The EWG heard there were two cases of anaphylaxis reaction on the first day of the UK vaccination campaign. The EWG heard there was also a case of supraventricular tachycardia, and investigations are still on-going, but the latest information suggests this case is unlikely to be associated with an allergic reaction. Currently ~½ million people have been vaccinated with BNT162b2 in UK and a further ~½ million have been vaccinated in the US.

2.2 The EWG heard the FDA have received reports of two cases of anaphylaxis: one severe and one of probable anaphylaxis, and a further two confirmed cases, one in Texas and another in Mississippi. MHRA are in discussions with FDA for how best to share the pharmacovigilance information about adverse events (AE) of interest such as anaphylaxis.

2.3 Subsequent to the two cases referred to above, the MHRA has received five more reports of anaphylaxis and three cases reporting “early anaphylaxis” or anaphylactoid reactions.

Three of these cases report treatment with intramuscular adrenaline and one reports treatment with adrenaline with the route of administration not provided. Detailed onset time are not available in three of the cases, and the remaining cases report events initiating in 20 minutes or less of administration of the vaccine. Including the original two cases, none of the cases have been fatal.

2.4 The EWG heard the information on previous allergies was reviewed, 3 cases included some history of allergy either to medicine, food, or related to an insect sting, 5 cases did not report previous allergic reactions.

2.5 The EWG heard that CPRD epidemiological data has identified 14 patients prescribed AAIs in the past year, who have also received the vaccine. Initial analysis has not identified the allergies which these auto-injectors have been prescribed for, nor the outcomes in these patients although data on any recorded events following these vaccinations should be available through data linkage in the future. There has not been significant reporting in Yellow Cards of allergic reactions in patients with AAI prescriptions. Detailed follow up further information requests have been made on the Yellow Card reports to determine the specific details of the suspected anaphylactic reactions, as well as steps taken to conduct further immunological analysis.

2.6 The EWG heard the company have conducted analysis of the medical history of BNT162b2 clinical trial participants in relation to allergy and hypersensitivity, and unblinded data on reports of drug hypersensitivity events. Overall, there was little evidence of an increased risk of anaphylaxis from the clinical trial data.

2.7 The EWG recalled that polyethylene glycol (PEG) was previously considered as a potential causative agent of the two allergic reactions seen in the vaccination campaign. The MHRA have conducted a review of other injectable medicines and some oral medicines that include PEG to see if similar adverse reactions have been reported. Caelyx pegylated liposomal, a liposome formulation of doxorubicin hydrochloride encapsulated in liposomes with surface-bound methoxypolyethylene glycol (MPEG), was considered to be the product most closely related to the vaccine in terms of the excipient formulation. The EWG heard there have been a significant number of anaphylaxis reports with Caelyx pegylated liposomal; however, due to the potential confounding with infusion reactions with this product it was currently not possible to establish causality. The EWG heard that other injectable pegylated products include warnings on hypersensitivity in their product information, although the contribution of PEG to the warnings is unknown, and the UK ADR reports do not show a consistent pattern of prior history of multiple allergic reactions. The EWG heard there is a paucity of data in the literature on PEG and allergic reactions, but it may exist as an under recognised condition. The EWG heard that the very limited number of Yellow Cards received that cite hypersensitivity or allergic reactions, given the high exposure (½ million doses administered), provides reassurance that cases of anaphylaxis remain rare, including when factoring in the known limitations of YC reporting.

2.8 The EWG noted that it is important to be clear that there is no difference between anaphylaxis and anaphylactoid reactions. Anaphylactoid reactions is an outdated term used to describe non-IgE-mediated anaphylaxis. Major international allergy associations do not recommend use of this term anymore to avoid confusion.

2.9 The EWG noted that incidence of anaphylaxis appears low and investigations of the UK cases of anaphylaxis are on-going; for one of the cases there is no signal that PEG is responsible. The EWG noted of the US cases, one patient had a possible route of sensitisation to PEG through potential contact with pegylated liposomal doxorubicin as part

of her professional duties as an oncology nurse. Overall, investigations are on-going, and are presently inconclusive as to whether PEG is the causative agent.

2.10 The EWG noted that prescription of an AAI does not preclude use of the vaccine, as there are other reasons to require one other than drug sensitivity, e.g. risk of anaphylaxis due to insect stings, latex, or other allergens.

2.11 The EWG noted a paper which identified the incidence of anaphylactic reactions to PEG to be uncommon; there have been 37 cases reported to the MHRA, but causality is not confirmed for all (Sellaturay and Nasser et al, 2020; J Allergy Clin Immunol Practice). Of the 5 cases of PEG allergy studied in the paper, some individuals reacted to injectable PEG, but anaphylactic reactions also occurred with orally administered medications containing high molecular weight PEG. In three of five patients clinically assessed, anaphylaxis was induced through intradermal testing with a minute quantity of PEG. The EWG also noted that anaphylaxis to PEG appears difficult to treat as the condition seems to persist and does not respond well to adrenaline.

2.12 The EWG noted blood from two of the three vaccinated UK patients who experienced anaphylaxis had been obtained, and the third is due 22nd December 2020. Testing will be delayed until after Christmas due to delays in obtaining the vaccine in the form needed. The EWG noted the FDA have prepared an assay for [redacted] and are collaborating with the UK in terms of immunological testing, but data is only expected after the New Year.

2.13 The EWG noted the possibility to conduct a differential analysis of infusion products containing PEG versus those that do not, such as rituximab. The data may assist with the understanding of causality in terms of infusion reactions versus allergic reactions.

2.14 The EWG was reassured that the signal of anaphylaxis does not appear to be strong.

2.15 The EWG noted that the food allergy may have adverse impact on vaccine uptake but there is little evidence for increased susceptibility to adverse reactions in this population. The EWG noted that patients with food allergies should not be deterred from taking the vaccine. In contrast patients with a history of allergy to PEG, must avoid the vaccine. The EWG heard that the SmPC section 6.1 and the section of the PIL for HCPs has been updated to make it explicitly clear that the product contains PEG while also listing the alternative name of the excipient, Macrogol.

2.16 The EWG noted that, the current pharmacovigilance data does not indicate an increased risk in those with a history of allergies to other vaccines, foods or medicines and therefore, this advice can be updated and aligned with the EMA advice. The EWG noted it was important to avoid causing confusion by updating the product information too regularly, but on this occasion, it was considered appropriate due to the number of doses administered since the original advice.

2.17 The EWG noted the importance of promptly referring YC reports to the immunology experts to enable additional investigation where agreed with the reporter. The EWG noted delays have been due the additional time needed to request further details as many of the original YC reports only included sparse detail.

2.18 The EWG noted skin reactions such as urticaria at a site or sites distant from the injection site would be termed systemic, as would any suspicion of IgE manifestation. A systemic reaction is likely to preclude giving a second dose of BNT162b2. The EWG noted if the signs of allergy are localised and also continuous with the injection site the second dose should be given. The EWG noted that any patient who has experienced a systemic allergic reaction

to the first dose of BNT162b2 should only receive a second dose on specialist advice, as dispensed by the clinic. The EWG also noted that a single dose of BNT162b2 gives a degree of protection against COVID-19, and so the benefit-risk of giving the second dose in cases where the patient is potentially sensitised to an ingredient/s in BNT162b2 is limited. Patients with suspected allergies to BNT162b2 need to be also warned against switching to the Moderna vaccine for the second dose as this vaccine also contains PEG. The EWG noted it is yet to be determined if the causative agent/s may differ between reported cases, and other excipients present in BNT162b2 are still being considered; therefore, it is currently premature to form opinions on vaccine switching.

2.19 The EWG heard the MHRA has also considered trace production excipients and concluded that these are unlikely to be causative agents. Further details will be provided to the immunology experts.

2.20 The EWG noted it is currently unknown if patients who have an allergic immunogenic response to the vaccine are protected.

2.21 The EWG noted that specialist expertise is required to accurately diagnose anaphylaxis, and there is a risk of error with use of the existing product information wording which places the onus on front-line healthcare professionals to make an assessment of the allergy history of the intended recipient. This also adds an unnecessary burden because the incidence of hypersensitivity and anaphylaxis appears to be very rare. The EWG noted it would be appropriate to align with the advice from EMA, Health Canada, and the FDA, this will have the added benefit of providing a consistent message. The 15-minute observation window will remain in keeping with the EMA label.

3. Paresis and facial paralysis with Pfizer-BioNTech COVID-19 vaccine

3.1 The EWG heard there are differences in the product information between that associated with the EMA centralised authorisation and UK authorisation under a regulation 174 in terms of capturing the adverse events (AEs) of facial paralysis reported in the clinical trial. The EWG heard 4 reports of facial paralysis occurred in the vaccine arm of the BNT162b2 trial with zero cases in the placebo arm, and one report of facial paresis occurred in the placebo arm with zero cases in the vaccine arm. The cases had varying times to onset from 2, 8, 36, and 47 days post vaccination.

3.2 The EWG heard that during the consideration of the Regulation 174 approval, events of facial paralysis were identified to be within the range of the background incidence rate, predicating the absence of an increased risk of acquiring facial paralysis due to the vaccine.

3.3 The EWG heard facial paralysis has been included, as an adverse event of special interest (AESI) under the term Bell's Palsy. The EWG heard on a related note, Guillain Barre Syndrome (GBS) is also an AESI due to previous concerns with the H1N1 vaccine; although subsequent epidemiological studies did not substantiate these concerns.

3.4 The EMA concluded there was at least a reasonable possible causal association with the vaccine, due to the imbalance between cases in the vaccine arm versus placebo, even though the frequency was within the background incidence rate. Therefore, the EMA included facial paralysis in the SmPC (4.8 undesirable effects) and one-sided facial drooping in the package leaflet, the SmPC includes a foot note stating the figures and onsets of these events as per the clinical trial data. The EMA have implemented the same pharmacovigilance measures as the MHRA in relation to these events.

3.5 The EWG heard that the YC data includes one report of facial paralysis submitted by a healthcare professional and one report of facial weakness submitted by a patient. Checks are being undertaken to confirm if the reports are duplicates, as the subject age and initials match. The results of an MRI scan are awaited, but a CT scan ruled out stroke. The EWG heard presently the rate of facial paralysis appears to be very low considering the exposure, but onset of the condition can be delayed to ~6 weeks post vaccination.

3.6 The EWG heard, in the Moderna clinical trial there have been 3 cases of facial paralysis in the vaccine arm versus no cases in the placebo arm.

3.7 The EWG noted the numbers are within the background rate, but this does not preclude the vaccine being the trigger. The EWG noted Bell's palsy and GBS are associated with viral infection and have been considered potential risks with other vaccines; GBS has been associated with other vaccines previously, although this was not supported by subsequent epidemiological investigation. The EWG noted that including the adverse event term in the UK product information may, beneficially lead to increased reporting of neurological events.

3.8 The EWG noted that Bell's palsy was associated with a liposomal vaccine administered intranasally for influenza, but this may not be connected (Mutch et al, 2004; NEJM).

3.9 Overall, the EWG noted that due to the imbalances seen in both the Pfizer and Moderna trials, and the additional YC report (possibly two), on a precautionary basis the UK Information for Healthcare Professionals and other relevant product information should be aligned with that produced by the EMA. The EWG noted that amendment of the current Risk Management Plan (RMP) was not required.

4. Update on BNT162b2 vaccine for use in pregnancy

4.1 The EWG heard that on 21 December 2020 the EMA granted a conditional Marketing Authorisation for the BNT162b2 vaccine. The information included in section 4.6 (fertility, pregnancy and lactation) and 5.3 (pre-clinical data) of the EU SmPC is marginally different to that found in the same sections of SmPC for the UK 174 authorisation and the text proposed for the UK Marketing Authorisation.

4.2 The EWG heard that the differences arise due to a preclinical reproductive toxicity study that was finalised after the authorisation under regulation 174. The study was conducted in female rats with BNT162b2 given by intramuscular (IM) injection prior to mating with an un-dosed male; the vaccine was also given on two occasions during pregnancy. The study design included caesarean section on gestation day 21 which would allow embryo-fetal malformations, if present, to be identified. A further group of rats was followed to litter and the behaviour and features of the offspring observed to post-natal day 21. The EWG heard the report concluded that the vaccine did not affect any of the parameters investigated in relation to reproductive health. The EWG heard the study supports breast feeding in women and raises no concerns for female fertility as there was no impact on: the ability of the rats to get pregnant, or on pregnancy viability. This provides reassurance of the safety and absence of effects from the nanolipid particles (NLPs) and the vaccine antigen.

4.3 The EWG heard immunogenic responses were seen in the dams, and the fetuses (at gestation day 21), and the pups (with exposure by occurring through lactation intake). The EWG heard in rats, exposure to the maternal antibody does not occur to any significant degree until late into pregnancy and this was identified as a possible caveat to the relevance of the study to pregnant humans. The EWG heard that rat organogenesis takes place approximately between day 10 to 15 and during this window there is probably minimal exposure of the fetus to the maternal antibodies generated in response to the vaccine.

Importantly, and in contrast to rats, the antibody exposure window in human embryos is earlier and in terms of vaccine-induced antibody exposure, the use of a rat model may not recapitulate the conditions needed to test if vaccine induced antibodies have an adverse effect on human fetal development.

4.4 The EWG heard there was an absence of a teratogenic effect in the rat fetuses, but the significance of this finding may be uncertain as regards human risk, considering there was likely to be little or no exposure to the vaccine induced antibody during organogenesis.

4.5 The EWG heard the EMA raised the issue in earlier questions to the company, and the company based their response on a meta-analysis (Bowman et al 2013, Birth Defects Research (Part B) 98:459–485). The meta-analysis found that placental antibody transfer (IgG) levels are relatively low during development after organogenesis but the ratio of maternal blood: fetal concentrations approach one by the end of gestation in multiple species including rat, rabbit, monkey, and human. The EWG heard the meta-analysis data collection commenced on gestation day 15, notably after the period of organogenesis ends in rat development. The EWG heard neither the study nor the meta-analysis support direct exposure of the antibody to the rat fetus during the period of organogenesis, consequently the statement “the vaccine is not teratogenic arising from its induced antibodies” cannot be excluded.

4.6 The EWG heard further studies in other species are not advised as the clinical data from incidental pregnancies in vaccinated individuals will be of greater scientific relevance.

4.7 The EWG heard the UK product information (that which is not applicable to the regulation 174) must align with the EMA, as the vaccine has now been authorised through the centralised route and the UK are currently within the EU; however divergence is acceptable if supported by evidence. The EWG heard the content in both versions of SmPC section 4.6 is similar and would not precipitate any change in clinical outcomes. The EWG heard section 5.3 includes additional information which is at a higher level of detail than is expected typically for this section, although the additional information is not contentious.

5. EWG discussion

5.1 The EWG noted the structure of the data provided does not include exposure data in the window of gestation day 6 to 15. The EWG noted that relevance to humans of the outcomes of the study have not been fully established. The EWG noted in terms of the preclinical regulatory requirements for a Marketing Authorisation, data would also be sought from other sources such as toxicokinetic information which has the potential to allay concerns about teratogenic effects.

5.2 The EWG noted that the degree of reassurance a negative signal in an animal model of reproductive toxicology gives is difficult to translate in terms of relevance to humans. The EWG noted that the importance of stating in the product information that the level of knowledge in terms of the interpretation of the reproductive pre-clinical data is limited.

5.3 The EWG noted in the field of paediatric immunology the current consensus is that placental IgG from the mother starts to be seen at gestation week 12 or 13 in humans. Organogenesis in humans ends by approximately week 8, and thus has elapsed prior to fetal exposure to maternal antibody, as such the risk of maternal vaccine induced antibody teratogenicity is likely to be low. The EWG, however, maintained that the direct relevance of the data from the rat study in terms of human pregnancy is nevertheless, uncertain.

5.4 The EWG noted antibodies to the spike protein will be generated through natural exposure to SARS-CoV-2, and this form of registry data may have some use to the topic discussed, but differences between antibodies produced by variants would need to be considered, as would differences in the vaccine induced antibodies versus antibodies generated due to natural exposure.

5.5 The EWG noted after the 31 December, Northern Ireland need to adhere to EMA labelling and product information, whereas Great Britain has the option to produce alternative text. The EWG noted that, wherever appropriate, it is important to maintain consistency.

5.6 Overall, the EWG noted that both the MHRA version of the SmPC and the EMA SmPC state there is insufficient evidence of exposure to the vaccine in pregnancy, but only the EMA SmPC provides for use in patients with an elevated benefit for receiving the vaccine e.g. pregnant women who are critically vulnerable to COVID-19. The EWG noted that there is no elevated risk to the public by aligning with the EMA wording, with the provision that it is made clear that relevance of the non-clinical reproductive data in human pregnancy is unclear, and that use during pregnancy must be an informed decision by the individual supported by the advice of a clinically qualified person/s.

5.7 The EWG noted that the UK information mentions that women of childbearing age should be advised to avoid pregnancy for at least two months after their second dose. The EWG heard the two-month period arose due to the time to clearance of the NLPs, but the clinical relevance to the embryonic or fetal development remains to be established. The EWG noted that this text should be removed due to the importance of a delivering consistent message. The EWG noted that to err on the side of caution, information on this topic could be communicated in other documents such as the patient group directions and immunisation protocols. Overall, the EWG noted that alignment of the product information and label was appropriate. The EWG noted, as part of the standard governing process, alignment of the product information and label will need to be considered at CHM.

6. AZD1222 clinical discussion and Q and A.

6.1 The EWG heard ChAdOx1 nCoV-19 vaccine uses a replication deficient chimpanzee adenovirus as a vector with the full-length gene for the SARS-CoV-2 spike protein inserted.

6.2 The EWG heard pre-phase I modelling suggested a single dose would be most effective to gain a signal of efficacy due to the high number of cases predicted at the time. Phase I commenced in April, however the number of COVID-19 cases was much lower than expected due to lockdown, and so the sample size was insufficient to give a signal of efficacy. However, a positive signal of stronger immune responses on neutralizing antibody was noted in a two-dose sub study so development was switched to a two-dose programme. An extended programme was conducted that confirmed the findings as well as the existence of T-cell responses to the spike protein.

6.3 The EWG heard phase II studies found little difference in the neutralising antibody titres between age groups induced with two doses; although levels were lower with a single dose, they were still similar between groups. Phase II and III studies were initiated in the UK, Brazil and South Africa plus a small phase I/II in Kenya which was not discussed. In the UK 11,000 participants are enrolled with 20% over 55, in Brazil 10,000 with 20% over 55. The partnership with AstraZeneca enabled 30,000 participants to be enrolled in the US with 25% over 65, in addition to small immunogenicity studies in Russia and in Japan, and India (completed). The EWG heard AstraZeneca share the vision to create a not-for-profit vaccine.

6.4 The EWG heard there was a manufacturing delay, which in turn delayed administration of the second dose to participants in the phase III studies, particularly to younger UK trial participants. Due to a lack of manufacturing capacity, the phase III trial material in the UK was sourced from a different manufacturer, a contract manufacturing organisation (CMO). The EWG heard the release assay for concentration of virus used by the CMO was different to that used by Oxford (PCR versus absorbance). The EWG heard a decision was taken to also apply absorbance testing to CMO produced batches as it is the most cautious approach and is consistent with the method used to release the Phase I material. The EWG heard participants in the phase III trial receiving the product from batches manufactured by the CMO had lower reactogenicity compared to phase I participants, and further investigations suggested carry over of polysorbate 80 interfered with the absorbance measure, the carry over resulted in a subgroup of 3000 participants receiving a half first dose termed low dose (LD), followed by a full second standard dose (SD), the subgroup is identified by the initialism (LD/SD). The majority of participants received a standard dose followed by a second standard dose (SD/SD group).

6.5 The EWG heard the efficacy endpoints are based on PHE and WHO symptom definitions published in February, with infection confirmed in symptomatic participants by PCR testing. Weekly swab-based PCR testing for all UK trial participants is also being undertaken to monitor asymptomatic infection. The EWG heard there is also an endpoint of serological evidence of infection that is yet to be analysed.

6.6 The EWG heard that 4th November 2020 was the data cut-off for the interim analysis with a database lock of 21st November. The EWG heard the results clearly showed that the reactogenicity of the vaccine which was more pronounced with the first dose. The other adverse events were evenly balanced between the vaccine arms and the control arms. The EWG heard serious adverse events across the 4 studies were 175 events in 168 participants, and three of these were considered possibly related to the experimental vaccine or the control vaccine. The first event was a case of haemolytic anaemia in the control group of the phase I/II study. The second was a case of transverse myelitis that was seen in a UK trial participant 14 days after the second dose (booster) of the experimental vaccine. This adverse event was considered possibly related to the vaccination by the investigator; the independent neurological committee review considered the most likely diagnosis was idiopathic short segment spinal cord demyelination. The third adverse event was a case of fever over 40^{o}C in a trial participant in South Africa; the fever resolved without hospitalisation and the participant received a second dose without a similar reaction. Due to blinding, it is currently unknown if the participant was in the control or experimental vaccine arm. The EWG heard there were two cases of neurological AEs that were determined to be unlikely to be related to the vaccine (control or experimental) by the independent neurological committee. One of the cases occurred 10 days after the first dose of the experimental vaccine, and on imaging, old lesions were identified consistent with the pathology of previously unrecognised, but pre-existing multiple sclerosis. The other case was in the control group.

6.7 The EWG heard the data from the phase I UK study and SA study was not included in the efficacy interim analysis due to too few COVID-19 cases post second dose. Overall efficacy results were 70% (from participants seronegative at baseline), LD/SD 90%, SD/SD: 60% in UK trial, and 64% Brazil trial. The EWG heard hospitalisation and severe COVID-19 data is available from the two clinical trials. Two cases in the vaccine group in first three weeks after first dose, one on the day of vaccination, the other at day 10, all subsequent cases were in the control group.

6.8 The EWG heard the package to support a potential Marketing Authorisation is based on the SD/SD regimen. The EWG heard protection was seen from 3 weeks after the first dose. The

EWG heard a post first dose interval of >4 weeks is supported by the data, up to 12 weeks; there was a trend that a longer interval may was associated with greater efficacy, and this is also supported by immunogenicity (serological antibody) data. The EWG heard there are relatively few older adults in the efficacy analysis, but further data is expected.

6.9 The EWG heard asymptomatic infection data in the LD/SD subgroup, saw a point estimate for VE of 58%, but with wide confidence intervals; in the SD/SD group there was a similar number of asymptomatic cases in each group.

6.10 The EWG heard the over 65s will be better represented in future analyses, as they were enrolled to the trial later. In the present analysis there are too few cases to draw firm conclusions on the point estimates of VE in the over 65s (8 control group versus 2 in vaccinated group from dose 1), but bridging antibody data to that reported from the Brazil trial leads to an estimated VE of 60%.

6.11 The EWG heard the results of the PCR testing have suggested the new SARS-CoV-2 variant is present in some UK trial participants and further analysis is being undertaken.

7. Questions and Answers

7.1 The EWG asked about the immunological basis of high VE in the LD/SD subgroup compared to the VE seen in the SD/SD group. The EWG heard immunogenicity analysis suggest that the high VE was more likely to be associated with the extended length of the interval rather than the dosing regimen.

7.2 The EWG heard the serological data consistently showed no strong association between anti-vector neutralising antibodies and the immune response to spike protein, but T-cell responses have yet to be excluded.

7.3 The EWG asked about implications for the differences in the purification procedure between the CMO and the Oxford site. The EWG heard differences were expected to be limited to null, as batches produced are comparable in terms of immunogenicity by batch, and amount of neutralising antibody. The EWG heard the vaccine given in the LD/SD and SD/SD groups of the UK trial are sourced from the same manufacturing batch.

7.4 The EWG asked about details and the outcome of a potential neurological AE reported in India. The EWG heard the independent neurological committee is currently reviewing the case. The committee's evaluations currently find a causal association between the study vaccination and clinical presentation to be uncertain. The clinical diagnosis put forth by the committee was of an acute and self-limiting non-specific encephalitis / encephalopathy with full recovery. Although, the committee is deliberating if the case is truly encephalopathic, as full recovery was seen without the use of immunomodulators—only antibiotics and antivirals. Further investigations are still on-going. The committee found high titres of anti-ribonucleotide (RNP) antibodies which may indicate lupus erythematosus (SLE); however, the committee identified no other clinical or systemic signs of SLE. Currently, two of the possible diagnoses are autoimmune disorders, or condition/s which respond to antivirals and/or antibiotics, but alternative diagnoses are not precluded at this stage.

7.5 The EWG asked if viral load in the SD/SD asymptomatic group had been measured to see if there was a reduction. The EWG heard normalising PCR against QC controls needs to be completed before analysis can be conducted in a robust manner. The EWG heard the new variant seems to be seen at higher viral loads, and how precisely, to factor this into the analysis also needs to be determined. The EWG heard that future data will potentially be

subject to confounding due to healthcare professionals in the control arm of the trial receiving the Pfizer/BioNTech mRNA vaccine (BNT162b2).

7.6 The EWG asked if the investigations of the case of transverse myelitis included measuring anti-neuronal antibodies and anti-vector antibodies. The EWG heard, there was extensive investigation of the case, there were no significant findings in terms of assessing auto-antibodies to the central nervous system (anti-neuronal antibodies not found). The EWG heard some members of the independent neurological committee correlate the pathology with a possible ischaemic event, which would align with a trip/fall reported by the participant.

7.7 The EWG heard serological testing revealed the presence of anti-vector antibodies but this finding was unremarkable as most vaccinated individuals possess anti-vector antibodies; how best to further interpret the data is currently not known. The EWG heard the changes were very anterior in the spinal cord and are only present in a single segment; of note the cerebral spinal fluid was also non-inflammatory. Overall, the findings are unusual, but an association with vaccine cannot be presently be excluded. A member of the EWG who was involved in the care of the patient, explained that the clinical pattern of disease onset and recovery was consistent with an inflammatory event rather than an ischaemic one, but the detailed information about the patient's recovery may still need to reach the independent neurological committee.

7.8 The EWG asked about the age distribution of the trial participants. The EWG heard that data from most of the over 65s was not available until beyond the cut-off for the interim analysis. The EWG heard the US study is enrolling 30,000 patients (including in Chile and Peru) and the target is 25% who are 65 and over. The data for the next analysis should be ready January / February.

7.9 The EWG asked about the immunogenicity in the context of duration post first or post second dose. The EWG heard that operation warp speed postulated that the difference in efficacy between the LD/SD and SD/SD was due to differences in immune responses to the vaccine in young versus old participants. The EWG heard this was likely to be incorrect because numbers of older patients included in the SD/SD group were very limited. The EWG heard the interval data support efficacy from an interval of 4 weeks and above, and there is a trend towards an incremental increase of efficacy with a longer interval between doses, and this is consistent with some other vector vaccines.

7.10 The EWG asked if the data to support use of prophylactic paracetamol were available. The EWG heard the study data from the phase II show that paracetamol does not have a detectable effect on immune responses to the vaccine.

8. AZD1222 Quality update

8.1 The EWG heard the content discussed relate to the application for a conditional MA; the batch specific release of AZD1222 under regulation 174 is to be discussed at a later meeting.

8.2 The EWG heard the material used in the clinical trials was derived from three manufacturing sites, and for each of the sites, the company have provided sufficient details of batch scale-ups and manufacturing process changes, as well as satisfactory justifications for significant changes.

8.3 To characterise the clinical trial product from the three sites, numerous analytical methods were employed by the company; [redacted]

[redacted] Assays of clinical trial product from each of the three processes results in functional S protein [redacted]. A comparability study demonstrated that the commercial Process 4 drug substance (DS) is comparable to DS from Process 1, 2 and 3 [redacted] although the limits are wide. The EWG heard other criteria are also very wide, however the data appear acceptable. The EWG advised that the company should commit to [redacted] for routine batch release.

8.4 The EWG heard an explanation of the process steps used to create the viral vector. The EWG heard the production steps were adequately described and the control of materials was acceptable. The EWG heard master virus seed (MVS) and working virus seed (WVS) for commercial manufacture were derived from a different lot of pre-GMP starting material to that used for the clinical trial lots, but at an earlier stage the material is traced back to the same protein & viral genome D8 isolate. The EWG heard this can be considered acceptable if DS lots are confirmed to be comparable. The EWG heard the company recently provided reassurance of comparability by undertaking additional DS characterisation in the form of NGS sequencing of the whole vector (including the S protein) and the results demonstrated 100% alignment with the reference sequence. Other forms of reassurance include the release specification parameters and other extended characterisation data.

8.5 The Company have also been asked to confirm the manufacturing site/s to supply the product to the UK, although this has been confirmed for the batch that may be procured under Regulation 174.

8.6 The EWG heard the DS control procedures appear adequate although full DS validation results expected soon are required.

8.7 The EWG heard an explanation of the drug product manufacturing process and controls, covering three separate manufacturing sites. The EWG heard the process and controls are adequately described, and the controls are appropriate although full DP validation data is also pending.

8.8 The EWG heard material of human origin and the materials of animal origin have been adequately described and the documentation including applicable risk assessments were considered suitable. The EWG heard that the adventitious agent screening and testing was comprehensive.

8.9 The EWG heard about the DS and drug product (DP) specifications. The EWG heard the specifications were considered appropriate, but all specifications will be revisited after additional manufacturing experience has been gained.

8.10 The EWG heard about the DP stability data programme: The EWG heard stability studies were conducted to establish DP shelf life at the long-term storage condition of 2-8°C. Data are available for up to 4 months at a storage condition of 2-8°C, for three clinical lots (Process 3) which are designated the primary stability lots, with supporting stability data from clinical lots derived from the other processes (1-2). The EWG heard stability studies have been initiated for seven Process 4 (commercial) DP lots. The EWG heard the proposed shelf life for the Drug Product is 6 months, the same as for the frozen DS. The EWG heard the shelf life is considered to be acceptable, but decreasing infectivity and increasing virus particles

vs infectious virus ratio, have occurred under accelerated stability testing and this was been noted as a potential aspect requiring further attention in case the company decides to extend the DP shelf-life beyond 6 months in the future.

8.11 The EWG heard the company had proposed an in-use shelf-life of 6 hours at room temp up to 30ºC and 48 hours in a refrigerator at 2-8ºC. The in-use shelf life was primarily supported by data from a microbial attribute study. The company have been advised by the MHRA to include an amendment to state that after first use the product should be used as soon as practically possible. The EWG heard the in-use shelf life should also be updated to clarify that the vaccine may be stored at 2-30ºC during the in-use period.

8.12 The EWG noted for an unpreserved product the best practise is to not go beyond a 6 hours in-use shelf life and that it is problematic to accurately record and track usage beyond 6 hours. The EWG noted that the 30ºC was not the room temperature value used in the stability studies, and 25ºC aligns with the Pfizer vaccine. The EWG noted the product should be used as soon as practically possible, to a maximum in-use shelf-life of 6 hours at 2-25ºC. The EWG noted that this in-use shelf-life corresponds to the most likely real-world in-use vaccination setting.

8.13 The EWG considered the [redacted] to be the most important measure of potency available, and therefore the [redacted] need to be introduced for the CMA. The EWG noted as a commitment to the conditional MA the DS and DP specifications (parameters and limits) must be appropriately configured in order to assure robust quality control.

9. Moderna Clinical Update

9.1 The EWG heard the vaccine (mRNA-1273) developed by Moderna consists of mRNA encapsulated in PEGylated lipid nanoparticles, with novel lipid excipients that are different to those in the Pfizer/BioNTech vaccine (BNT162b2). The EWG heard the vaccine includes a single mRNA sequence encoding the pre-fusion stabilised Spike (S) protein of the SARS-CoV-2 virus.

9.2 The company have applied for a conditional Marketing Authorisation for their vaccine. The proposed indication is active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals18 years of age and older. The vaccine is given as two intramuscular doses of 100 micrograms with an interval of 1 month between each dose.

9.3 The EWG heard immunogenicity data are available from phase I and II studies, but the phase I study was sponsored by National Institutes of Health (NIH), and therefore reports on the validation and qualification of the methods are not available. The data was still considered to hold importance, due to the extended duration covered; three months post second dose. The EWG heard that a dose response was seen between 25 and 100 micrograms, and the proposed dose of 100 micrograms was based on these data.

9.4 The EWG heard there was a reduction in levels of binding and neutralising antibodies at 3 months post dose 2 in the older participants, but the levels still exceeded those of convalescent sera.

9.5 The EWG heard the cellular response data has been requested from the Company.

9.6 The EWG heard of a phase 2a, randomised, observer-blind, placebo-controlled safety and reactogenicity study of mRNA-1273 SARS-CoV-2 vaccine in healthy adults aged 18 years

and older, sponsored by the applicant. Two age group cohorts were planned: ≥18 to <55 years (n=300) and ≥55 years (n=300). The EWG heard participants were randomised to three dose groups (1:1:1): mRNA-1273 50 µg (n=200), mRNA-1273 100 µg (n=200) and 0.9% sodium chloride placebo (n=200), i.e. 100 participants were planned for each age/dose group. Vaccine or placebo was administered by 2 injections of 0.5 mL into the deltoid muscle 28 days apart. The EWG heard humoral data from the study are presently available. The EWG heard that there was not a large difference in neutralisation responses between the age cohorts, the EWG heard at the at the 100µg level, a large humoral response is seen two weeks after dose two, and the data to 1 month shows this response is sustained.

9.7 The EWG heard clinical efficacy data have been generated from a single pivotal Phase III study that was a standard design similar to those employed by other companies developing vaccines to protect against COVID-19. The study was only conducted in US and has enrolled ~30,000 participants aged 18 years and older with no known history of SARS-CoV-2 infection rather than COVID-19, the equivalent exclusion criterion employed by the Pfizer BioNTech study. Clarification has been sought to confirm if all-comers are included in the Moderna trial. The participants were randomised 1:1 to receive 100µg of mRNA-1273 vaccine or placebo, as 2 doses separated by 28 days. The EWG heard the trial did not include immunosuppressed patients and those receiving concomitant vaccination were excluded.

9.8 The EWG heard the applicant has been asked to clarify if history of allergy, anaphylaxis, or urticaria, is to any agent, or specific to the vaccine / any of the vaccine's ingredients. The EWG heard baseline medical history will also be requested to assess how many participants have a history of allergies, due to the contextual background of two anaphylaxis cases occurring shortly after vaccination with the lipid nanoparticle mRNA Pfizer/BioNTech vaccine.

9.9 The EWG heard more than 50% of participants randomised have completed 2-month post second dose follow-up; within this 25% are over the age of 65 and some patients over 75, the proportion of SARS-CoV-2 positive participants was similar to that seen in the Pfizer/BioNTech trial, but an increase to 5% is predicted to be confirmed by further results. The EWG heard that key patient groups were well represented in the study population.

9.10 The EWG heard that at the final analysis,196 cases of COVID-19 have been reported in the trial: 11 in the experimental vaccine group and 185 placebo group (out of ~14,000 total participants per group). The vaccine efficacy (VE) is calculated to be 94.1% similar to that seen in the interim analysis, and within the confidence limits and VE target set by WHO.

9.11 The EWG heard VE of 86.4% (4 experimental vaccine, 29 placebo) was reported from the subgroup of participants age 65 and above (3500 participants per group). The EWG heard VE was found to be similar in the age 75 and above (0 experimental vaccine, 7 placebo) (650 subjects per group)

9.12 The EWG heard in non-white participants the VE is also high at 97.5% (5000 subjects per group).

9.13 The EWG heard VE was also high in subjects at high risk of severe disease ~90%, the VE values are also included in the data package associated by each risk factor, individually. The EWG heard further VE data is requested following dose one.

9.14 The EWG heard all cases (30) of severe disease have occurred in the placebo arm, and the one death from COVID-19 has occurred in the placebo arm.

9.15 The EWG heard about the clinical safety data. EWG heard that the Phase I and II studies predominately enrolled healthy volunteers, whereas the pivotal phase III study enrolled a boarder population. The phase III study was identified as the most important source of reactogenicity data. The EWG heard two datasets were reviewed, one with a data-cut point of 11 November 2020, median follow-up of 49 days after the second dose, and 25 November 2020, median follow-up 63 days after the second dose. The company plan a database lock on 25 December 2020; and corresponding study report to be finalised by March 2021. The SmPC will currently reflect the 11 November cut off as the 25 November is still under review. If a conditional Marketing Authorisation is granted, the subsequent safety data from the cut off of 25 Nov and database lock on 25 Dec will be introduced by a variation procedure.

9.16 The EWG heard the Phase III recorded solicited adverse reactions (ARs) from 14,500 participants in each treatment group. The EWG heard there was a high incidence of local reactions: pain, swelling, erythema, and ipsilateral axillary lymphadenopathy. Zero grade 4 local reactions were reported and of the grade 3 local reactions, the most severe was pain at the injection site. The EWG heard the incidence of systemic reactions was also high. The systemic ARs included 14 grade 4 events of which 13 were cases of fever in the vaccine arm vs three cases in the placebo arm, and one was a case of nausea and vomiting in the vaccine arm vs none in the placebo arm.

9.17 The EWG heard most ARs were mild to moderate and occurred on day 1-2 of vaccination and lasted for a median of 2-3 days, with some reactions persisting beyond 7 days. ARs were more frequent after the second dose. The EWG heard overall, the safety profile of mRNA-1273 is consistent with that of BNT162b2, especially in terms of the pattern of ARs myalgia, pain (injection site), fever, chills, and fatigue.

9.18 The EWG heard that the incidence of serious adverse events (SAEs), fatalities and discontinuations due to AEs were similar in the vaccine arm and placebo arm. Analysis of related SAEs identified two cases of facial swelling in participants who had previously received cosmetic facial injections (case 1: botox, case 2: hyaluronic acid) are likely to be related to the vaccine, this information will be included in section 4.8 and 4.4 of the SmPC.

9.19 The EWG heard there are some adverse events of special interest (AESIs): Bell's palsy (3 active, 1 placebo, two of the cases in the vaccine arm had co-infections) and arthritis (11 active 3 placebo, two in the vaccine group considered possibly related), the AESIs could not be confirmed or excluded to be related to the vaccine with certainty and these should be reviewed closely in future safety updates. The EWG heard there was also a slight imbalance in cases of hypersensitivity reactions (1.5% vaccine 1.1% placebo) mainly explained by injection site urticaria and injection site erythema. The EWG heard that to date, there have been no reports of anaphylaxis which have occurred in the immediate aftermath of administration of the vaccine. There was one report of anaphylaxis 11 days after first dose considered not related. There were 233 cases of allergic or hypersensitivity reactions; of these cases seven patients were withdrawn from receiving the second dose. The clinical features of the seven cases were: swollen lips, or urticaria, or a rash at the injection site immediately after administration or one that persisted for a long duration. Of the 233 cases, 10 had events reported after the second dose but with no increase in severity of the reaction/s.

9.20 The EWG heard there were no specific safety concerns, including no evidence of enhanced COVID-19, and adverse events were well balanced between the active arm and placebo with a greater proportion of AEs occurring in the younger among the clinical trial population compared to the older sub-groups; reassuringly AEs were less frequent and less severe in seropositive individuals.

9.21 The EWG heard that overall, the safety profile has been adequately characterised and is found to be acceptable. A few areas of uncertainty such as long-term safety and safety in populations excluded from the studies need to be monitored in the ongoing studies and in the post-authorisation setting.

9.22 The EWG heard of the measures and content associated with the RMP.

9.23 The EWG noted slight differences in the product information wording regarding use in pregnancy between the COVID-19 vaccines developed by Moderna and Pfizer and advised that international regulatory consistency should be strived for across the vaccines. The EWG noted that pre-clinical data is yet to be reviewed by the EWG.

9.24 The EWG noted the impressive rates of VE, especially those seen in the elderly. In agreement with the assessment team, the EWG noted drug hypersensitivity exclusion criterion should be clarified. The EWG also noted that~17% of recipients in the phase II trial are recorded as having baseline drug hypersensitivity, further investigation of this group may give a better understanding of the propensity for the vaccine to induce allergic reactions in those with a history of medicine allergy.

9.25 The EWG noted VE was high including across subgroups such as those with risk factors for severe disease. The EWG noted there is a variety of measures of VE employed by the different Sponsors of vaccines, the EWG noted that the VE seen in the Phase III was substantiated by the use of a secondary analysis which utilised another measure of efficacy, in addition to the primary measure (hazard ratios). The EWG noted it would be useful to investigate the 11 cases of vaccine failure, as this could improve the characterisation and limitations of the protection acquired through use of the vaccine.

9.26 The EWG noted the clinical data supporting mRNA-1273 and that supporting BNT162b2 appears consistent across many aspects and drawing conclusions on comparability is feasible.

9.27 The EWG noted that Professor Tom Solomon should be contacted for his views on cases of facial palsy.

10. Future Steps / Any Other Business

10.1 None.

11. Date and time of next meeting

Thursday 24th December 2020 at 10:30

The Meeting started at 11:30 and ended at 15:30

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.