NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 15th February 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan
Professor N French[1]
Professor D Goldblatt[2]
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson[2]
Professor P Shah
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor T Solomon

Member of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh[1]

Invited Expert

[redacted][3]

Observers

[redacted]

Secretariat

[redacted]

[1] Left during item 9
[2] Left during item 8 & [3] supporting specific items

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

MHRA Presenters supporting specific items[3]

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - VRMM
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Dr S Branch - VRMM
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[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - MHRA-Policy
[redacted] - LD
Mr K McDonald - LD
Ms T Moore - IE&S
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
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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
IE&S = Inspection, Enforcement & Standards

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 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 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 – 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 Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of 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 Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. 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. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent

one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

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

1.4 Apologies were received from Professor Solomon for the meeting today.

1.5 The Chair welcomed [redacted] from PHE as an Invited expert for Item 2 - Update on Impact Surveillance. [redacted] left the meeting after his presentation.

1.6 The Chair also welcomed [redacted] of HSCNI and [redacted] of Public Health Wales as Observers for Items 4 & 5. The Observers left after item 5.

2. Update on Impact Surveillance

2.1 The EWG viewed slides and heard a presentation from Public Health England (PHE) on an update on Impact Surveillance. A presentation three weeks earlier consisted of analysis on Pillar 1 and Pillar 2 routine testing data. This update concerns data analyses from Pillar 1 and Pillar 2 data, SIREN (Sarscov2 Immunity and REinfection EvaluatioN) study data, the Severe Acute Respiratory Infection (SARI)-Watch surveillance system and the Royal College of GP (RCGP) Database.

2.2 Pillar 1 and Pillar 2 update

2.2.1 The EWG heard an update on the analysis of available Pillar 1 and Pillar 2 data; the data is linked to the National Immunisation Management Service (NIMS) database. The focus of the analysis was vaccine effectiveness (VE) for Pfizer and AstraZeneca (AZ) vaccines, rather than any impact analyses data.

2.2.2 The EWG heard that the Pillar update includes new data for AZ, the over 70s cohort population, analysis of cohorts with repeat testing and care home analysis.

2.2.3 In summary, PHE reported that VE against symptomatic diseases reaches 60-65% in the over 70s and ≤ 65 HSCW (health and social care workers) after the first Pfizer dose. There is a continued apparent reduction from day 35, but continued monitoring is required to discount any possible bias. After the second Pfizer dose, VE reaches approximately 85% in the over 70s and approximately 90% in < 65 HSCW. The VE of the AZ dose against symptomatic disease was shown to increase from 21 days.

2.2.4 EWG also heard that interim analysis of the data showed (i) preliminary evidence of VE against infection from Pfizer vaccine in HSCW (stronger evidence provided in the Siren data,

see below) and care home residents (ii) preliminary evidence of VE against infection from AZ in HSCW but not yet in care home residents (iii) Evidence of reduced mortality in vaccinated cases (Pfizer).

2.3 SIREN update

2.3.1 EWG heard that for this update the vaccination data sources were National Immunisation Management Service (NIMS) dataset and self-reporting via Siren questionnaires.

2.3.2 EWG heard that participants were assigned to cohort based on baseline antibody status (at 07 December 2020); positive cohort participants - antibody positive or evidence of infection and negative cohort – antibody negative and no previous positive test. The outcome for analysis was infection (positive Polymerase chain reduction test; PCR+) in the negative cohort.

2.3.3 EWG heard that this study had better defined cohorts of under 65 HSCW than that found in the Pillar cohorts.

2.3.4 The EWG heard that the Siren interim data showed vaccine effectiveness of 60-74% against infection at 21 days after a single dose of Pfizer vaccine in the negative cohort. The invited PHE expert indicated that future analyses may include symptomatic infection and hospitalisation.

2.4 Cohort analysis within the Royal College of General Practitioners (RCGP) Database

2.4.1 EWG heard that PHE conducted an analysis within the RCGP database, which is a General Practitioner (GP) cohort dataset. This database allows adjustment for more variables than is possible with the Pillar data, while still using the PCR-positive data that arise from the Pillar data. Initial analyses included the 80+ population, over the period 07/12/2020 – 24/01/2020 who tested PCR-positive and had a GP consultation with symptoms/clinical illness consistent with COVID-19 around the time the test was taken. This was compared against a Test-Negative Case Control (TNCC) data set.

2.4.2 PHE concluded that the results from analysis were broadly consistent with routine testing data. VE after one dose was 60-65% and 50% for the TNCC cohort. After two doses, vaccine effectiveness was 85% and 70-75% for the TNCC cohort.

2.4.3 The invited PHE expert indicated that future analyses would focus on VE within clinical risk groups.

2.5 SARI-Watch surveillance system

2.5.1 EWG heard that the Severe Acute Respiratory Infections (SARI)-Watch is the surveillance system for new Covid 19 hospitalisations.

2.5.2 EWG heard that analysis was restricted to elderly with Covid with symptoms. Hospitalisations were matched against the National Immunisation Management Service (for vaccination status with the Pfizer vaccine), age, sex, geographic region and period. The data was not adjusted for care home residents.

2.5.3 PHE reported that preliminary evidence shows that Pfizer vaccine is effective at preventing hospitalisation in patients in the 80+ age group (75%-80% reduction), compared to those that had not been vaccinated. It should be noted that the low number of hospitalisations seen immediately after vaccination is likely related to the deferral effect, where patients testing positive for Covid-19 or showing symptoms have their vaccinations deferred.

2.5.4 The invited PHE expert concluded overall that the preliminary evidence showed that the Pfizer vaccine was effective in preventing hospitalisations and that evidence through the Pillar 2 mortality analysis showed a lower risk of death in recipients of the Pfizer vaccine.

2.5.5 The PHE expert commented on the potential biases that cause the differences between real world data and trial data.

2.6 EWG discussion/comments

2.6.1 EWG asked whether the invited expert was able to link the efficacy data to variants. PHE stated that early data reflect the older variants and the majority of the data now emerging is against the newer variants. EWG heard that PHE does receive some data from the Lighthouse labs that would allow split along the lines of efficacy against older and newer variants. However, this sub-set of the data shows the same effect, but with wider confidence intervals.

2.6.2 EWG asked the PHE expert whether analysis of the Royal College of General Practitioners (RGCP) data was possible to look at effects on recipients of the vaccine who are on immunosuppressants. The invited expert indicated that this analysis would be conducted alongside other collaborators and result were expected soon.

2.6.3 EWG were interested in possible data to show whether protection is seen a few days after vaccination, which could be related to an adjuvant effect and could be very important to patients who are immunocompromised. The PHE expert thought that there is potential for a lot of bias in the day 0 to 3 data, but that interesting data regarding the severity of symptoms could be shown.

2.6.4 EWG asked for further information on the relationship between immunogenicity and the efficacy of the vaccines, given that some data show that immunogenicity (antibody levels) is lower in the over 65s. The PHE expert stated that they would like to see more antibody data in the over 65s before coming to any conclusions. However, the PHE expert stated that their efficacy results in the over 65s were higher than those seen in the Real-time Assessment of Community Transmission (REACT) study results.

2.6.5 EWG commented that it will be interesting to see the data for the end of February/start of March, i.e., when recipients who received their first dose at vaccine rollout will reach 12 weeks and receive their second dose.

2.6.6 EWG commented on parallel analyses conducted in Scotland and England, where the dataset reliably identified subjects that were known HSCW at time of test. Within this subset, the response was consistent with that presented by PHE over the interval 21 days- 6 weeks. As they have a fifth of the population, the dosing interval is wider in Scotland; however, the pattern is similar.

2.6.7 EWG stated that they looked forward to the next update.

3. Proposed statement on "flu like illness" for Pfizer/BioNTech and AstraZeneca COVID 19 vaccines – Verbal update

3.1 The meeting heard that flu like illness is a recognised side effect of the vaccines, and the EWG had previously discussed and agreed that further communication on this side effect was required to better inform patients on how this might present in patients. The EWG were presented with proposed wording to further characterise "flu like illness" in the information

for UK recipients and healthcare providers for the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines, and for a similar statement to be included in the ADR data publication.

3.2 The EWG supported the inclusion of this statement and the EWG noted that it was important the information was worded in way that would be reassuring to recipients and that the advice is consistent with information provided in other patient leaflets on COVID-19 vaccination produced by the UK healthcare agencies. The EWG considered that the event of heart palpitations required further characterisation before it should be included in the product information for the vaccines.

4. Safety update on Pfizer/BioNTech COVID-19 vaccine

4.1 The EWG was presented with a second safety update for the Pfizer COVID-19 vaccine. The EWG was informed that the ADRs being reported for the vaccine were broadly in line with the known safety profile for the vaccine and that seen in the clinical trials. The EWG also heard that the signal of Bell's palsy has persisted in the observed/expected analysis and that the planned formal epidemiological study was progressing. The EWG were informed that the possible signal of myo/pericarditis which had been detected in the Rapid Cycle Analysis has continued to diminish and was likely a chance finding. The meeting discussed that there was a slightly lower reporting rate in the past month compared to previously and was reassured that promotion of the scheme was ongoing.

4.2 The meeting was presented with a summary of the anaphylaxis reports received through the Yellow Card scheme and related international data, and that the nature and frequency of events is similar to that reported previously for the Pfizer/BioNTech. The meeting discussed concerns from healthcare professionals and the JCVI COVID-19 subcommittee on the risk of transmission related to the 15-minute observation period which was introduced following initial reports of anaphylaxis with the Pfizer/BioNTech COVID-19 vaccine. The EWG acknowledged the practical constraints of the observation time and representatives from HSCNI and PHW noted that there was no direct evidence of increased COVID-19 transmission due to the waiting time. The EWG highlighted that there was limited data on the risk of anaphylaxis with the second dose. The meeting concluded that the 15-minute wait should remain in place until more data is available to support its removal.

4.3 The meeting concluded that of the data presented overall in the safety update that no new safety signal has been identified.

5. Review of fatal reports for the AstraZeneca and Pfizer/BioNTech COVID-19 vaccines

5.1 The EWG was presented with a paper which gave an overview of fatal reports received by MHRA to date. The paper presented cumulative vaccine exposure, broken down by age and discussed the analysis MHRA has performed on fatal reports, as well as international data available. The EWG noted that observed/expected analysis did not indicate an excess of deaths; however, it was acknowledged that these analyses are used with caution to assess mortality.

5.2 The meeting broadly found the data reassuring. It was noted that there was significant under reporting of fatalities to the Yellow Card Scheme and that there can be difficulty in interpreting the data where reports are sparse. The EWG discussed whether Hospital Episode Statistics data could be used to support Yellow Card data but noted that there is a 3 month lag to this data.

5.3 The EWG agreed with the conclusion that there was not a signal indicating an increased risk of death following vaccination.

6. Regulatory approach to new variants – feedback from international regulators' meeting

6.1 The EWG were informed about recent discussions held with other international regulators. While there is broad agreement about a more tailored approach to regulating SARS-Cov2 vaccine variants, it was highlighted that the draft MHRA guidance document required more discussion in its non-clinical and clinical sections. For the non-clinical section, experts emphasized the novelty of the coronavirus and the need, in principle, for a sufficiently large non-clinical database overall. It was appreciated, however, that the extent would depend on the knowledge already gained and the particular format of a given vaccine, and therefore agreed on an approach where absence of non-clinical data, including immunogenicity, will have to be justified by the Applicant. It was agreed that generation of non-clinical data should not delay the development and introduction of updated coronavirus vaccines. It was highlighted that SARS-Cov2 variants which are adapting to humans may be less pathogenic in animals, rendering animal challenge studies less straight-forward.

6.2 For the clinical part, the Expert Group noted that MHRA does not propose to ask for head-to-head non-inferiority studies on neutralising antibodies, but rather asks for studying humoral and cellular immune response (including neutralising antibodies) with the new variant, comparing with a panel of convalescent sera. Experts broadly agreed with this approach, in absence of knowledge of a meaningful non-inferiority margin.

7. Supply of AZ vaccine from SII

7.1 The EWG viewed slides and heard a presentation from MHRA concerning a paper assessment of an application under Regulation 174 (R174) to approve three named batches of ChAdOx1 nCov-19 vaccine from the Serum Institute of India (SII), a major facility in India, for use in the UK national vaccination programme. The assessment has been expedited to approve before the shelf-life expiry is reached.

7.1.1 The EWG heard that Covishield was developed in collaboration with Oxford University and AstraZeneca (AZ). The technology to manufacture this vaccine along with virus seed and cell banks were received from Oxford/AstraZeneca. The product has been approved in 10 countries and 34.5 million doses have been distributed worldwide by the end of January 2021.

7.1.2 The EWG heard that SII has provided MHRA with full Modules 1, 3 and 5 of the dossier, and some additional batch release data for the three named batches. The full-scale 2000 litre batches will be manufactured on two different lines in the SII facility.

7.1.3 The EWG also heard that AstraZeneca has transferred manufacturing process and key analytical methods for Covid-19 ChAdOx1 vaccine to SII. There have been some changes to manufacturing, however with no material effect to the product.

7.1.4 The EWG heard that manufacturing and testing of the seeds/banks appear largely acceptable, but some questions are raised re methods validation/missing reports. Questions have also been raised concerning testing for adventitious agents.

7.1.5 The EWG heard that the specifications for drug substance and drug product are almost identical to AZD1222. Data submitted confirm R174 batches conform to AZ R174 specifications (SII has provided a commitment to adhere to the AZ specifications previously approved as per R174). Analytical methods/validation were also assessed as generally acceptable.

7.1.6 The EWG heard that satisfactory stability data for 4 weeks at 2-8°C have been presented for the drug substance and inspection feedback confirms acceptable on-site procedures for storage and transportation within the facility. Currently limited stability data is available for the drug product; further stability data has been requested. The proposed shelf life is 6 months at 2-8°C The regulation 174 batches were manufactured in October 2020, and therefore, MHRA would require additional assurance over stability before these batches can be accepted with a > 6 -month shelf-life. The in-use shelf-life of 6 hours stored at 2 to 25°C is acceptable.

7.1.7 Concerning the dossier, MHRA concluded that subject to satisfactorily resolving the requests for further information (RFIs) the product demonstrates sufficient comparability to the Oxford/AZ vaccine, the manufacturing process is reproducible, and in control and the dossier provide sufficient data concerning safety of the product. However, additional stability data is required before an increased drug product shelf life can be assigned. Further, safety of the batches with regards to adventitious agents needs to be assured. The MHRA considered that if all RFIs are resolved (some immediately, some as a commitment), these R174 batches could be approved and could be labelled as AZ batches.

7.1.8 The EWG heard that SII is making/planning future changes to the manufacturing process, mainly related to changes in fermentation parameters (SII Process IV) and will make it more similar to the AZ Process IV. The process is currently undergoing validation with tentative completion late February 2021.

7.1.9 The EWG also heard the MHRA assessment of the interim report of the immunogenicity and safety bridging study performed in India (Interim CSR) submitted to support the application. EWG heard that safety data has been provided from 1600 subjects who received at least one vaccination with either Covishield (1200), placebo (300) or AZD1222 (100) in the immunogenicity and safety study. Reactogenicity was assessed in the same subpopulation as immunogenicity. The immunogenicity results indicate that Covishield can be considered noninferior to AZD1222 vaccine. In summary, there are no concerns about the safety of Covishield and its reactogenicity is broadly comparable to that of AZD1222.

7.1.10 MHRA requested whether EWG agrees that (i) the three named batches to be approved under R174, if RFIs are resolved and appropriate conditions are imposed (e.g. independent batch release, etc), (ii) that MHRA approves individual SII batches on the basis that they have consistent quality and production with the batch data obtained for the R174 batches, (iii) assuming the committee agrees to point (ii) would the committee wish to re-discuss regarding individual batches produced by the updated SII process (SII Process IV) before MHRA approved them.

7.2 EWG comments/discussion

7.2.1 The EWG asked the MHRA for an update concerning inspection of the facility. EWG heard that the MHRA-GMP inspection has been conducted and is to be concluded with the company imminently. No critical deficiencies had been raised and the conditions for supply would follow normal Marketing Authorisation Application routes (importation testing would be required and independent batch release by NIBSC would be specified in the conditions).

7.2.2 The EWG also requested an update from NIBSC regarding batch testing. EWG heard that NISBC had received samples of the R174 batches, and these were currently on test. NISBC assured the EWG that the same suite of testing as performed on the AZ vaccine would be applied to the R174 batches and the batches would also be tested against the AZ specifications (with respect to product appearance, the identity and the infectivity). Test results are expected later this week.

7.2.3 The EWG asked why these batches have become available, seeing that these batches are coming out of a geographical area which would be expected to have great need for these vaccines (India). The EWG was informed by MHRA-LD that the R174 batches were coming towards the end of their shelf life and run the risk of going out of date; it was considered that the UK, more so than others, have the logistics to deploy them quickly. NIBSC further commented that the MHRA had experience testing product from SII and results had been reassuring.

7.2.4 The EWG discussed the issue concerning the remaining shelf life on the product and concluded that the issue of deployment was outside the remit of the MHRA.

7.2.5 Concerning the quality data provided, EWG considered that overall, the quality aspects of the three discussed batches were acceptable once a small number of issues related to pathogen safety were satisfactorily resolved. These must be resolved before the batches are approved. The remaining concerns can be resolved as commitments. EWG was reassured, for the present time, that the clinical, immunogenicity and safety data is generally equivalent to the AZ vaccine.

7.2.6 The EWG endorsed the MHRA recommendations concerning approval of the R174 batches; once relevant quality issues are satisfactorily resolved EWG endorses the application being forwarded for CHM consideration for approval under R174. Further, EWG confirmed that there was no need for EWG to re-discuss individual batches produced by SII Process III or IV before MHRA approve them.

8. Updated efficacy analysis of AZD1222 vaccine and updated UK information for HCPs

8.1 The EWG was presented with an updated efficacy analysis based on the 07-12-2020 data cut off and which included all four studies (Cov001, -002, -003, and -005). This analysis will be presented in the updated UK Public Assessment Report (UKPAR) and updated Information for Healthcare Professionals (HCPs). The primary endpoint of vaccine efficacy was 66.7% (95%Confidence Interval [CI] 57.4, 74.0) with no severe cases/hospitalisations in the vaccinated participants. The efficacy with a dosing interval ≥ 12 weeks was 80.0% (95%CI 65.2, 88.5). Analyses incorporating both asymptomatic positive and symptomatic positive cases in the UK COV002 trial were further explained to show that the vaccine is reducing not only the proportion of symptomatic cases, but also the overall proportion of PCR-positive cases. This shows that the vaccine is reducing the transmission rate.

8.2 Apart from updated efficacy and immunogenicity data in the UK Information for HCPs, there will be changes to the safety data presented with the addition of anaphylaxis and diarrhoea in the list of Adverse Drug Reactions (ADRs) and corrections of frequency in a few reactogenicity ADRs. Slight differences in the safety sections with the EU-approved SmPC were highlighted, the main one being that in Section 4.4, the EU SmPC recommendation of close observation for at least 15 minutes following vaccination, in line with the other approved vaccines in the EU.

8.3 EWG comments/discussion

8.3.1 The EWG asked whether updated data was available from all studies on the median duration of follow-up following administration of the two vaccine doses. MHRA indicated that this information was currently awaited, as confirmation of the median duration of follow up had already been requested from AstraZeneca.

8.3.2 The EWG also raised concerns that the control arm of the study would have a diminishing number of subjects with time, as they are vaccinated in line with their national vaccination schemes. MHRA has confirmed that this is the case. The EWG asked for confirmation from

AZ of what they would be doing with their control arm in the future. MHRA confirmed that a protocol amendment to the UK studies had been approved to that effect.

8.3.3 One EWG member commented that anecdotal feedback received from patients would indicate that information being provided by health professionals to patients at the time of vaccination is inconsistent with scientifically established information, e.g. patients have reported being informed that vaccine effectiveness post vaccination is 2 weeks rather than 3 weeks. EWG recommended that MHRA liaise with the public health bodies to ensure clearer, consistent, unequivocal information is provided to patient concerning vaccination and vaccine effectiveness.

8.3.4 Overall, it was agreed that the UKPAR and the HCPs should be updated with the new information.

9. Analysis of ADZ1222 vaccine against new variants

9.1 The EWG was presented with recent results (submitted for publication) of AZD1222 vaccine against SARS-CoV-2 variants.

9.2 The first paper relates to the UK variant B.1.1.7. Vaccine recipients had neutralisation titres 9-fold lower against the B.1.1.7 lineage than against the Victoria lineage. However, the UK COV002 study showed an efficacy of 75% against the B.1.1.7 variant compared to 84% against the other variants to prevent symptomatic disease and an efficacy of 67% compared to 81%, respectively, to prevent any SARS-CoV-2 infection. An evaluation of viral load in the nasal swabs showed lower viral load in vaccinated participants compared to controls and in asymptomatic subjects compared to symptomatic subjects. Likewise, the duration of positivity of nasal swabs was shorter in vaccinated participants compared to controls and in asymptomatic subjects compared to symptomatic subjects. It was not different between the B.1.1.7 and non-B.1.1.7 variant cases.

9.3 The second paper relates to the South-African variant B.1.351. A [redacted] assay performed in 19 seronegative vaccinees showed that, out of 18 participants with neutralisation activity against B.1.1, 10 (56%) had undetectable neutralisation activity against the B.1.351 variant and the remaining eight showed a 2.5 to 31.5-fold relative reduction in neutralisation. The South-African COV005 study showed an overall efficacy of 22% whereas most cases (39/42) were due to the B.1.351 variant. In contrast, the efficacy after the first dose until 31.10.2020 (i.e., before circulation of the SA variant), a proxy for non-B.1.351 variant infection, was 75%, in line with the UK results.

9.4 EWG discussion/comments

9.4.1 The EWG considered that the data relating to the UK variant was reassuring. The EWG noted that whilst the data regarding the SA variant was more concerning, it is unknown yet whether the vaccine could still protect against severe disease. Given the age of the participants (median of 31 years), the SA trial is unlikely to address this question. The EWG also discussed the current thinking in relation to the role of T cells in the response to SARS-CoV-2, and in particular, that T cells may be more important in protection against severe disease. It has been proposed that T cell response may be preserved against variants due to cross-reactivity of T cell epitopes although what this means clinically is not yet known.

10. <u>Any Other Business</u>

10.1 None.

11. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 25th February 2021 at 12:30.

The Meeting today started at 10:33 and ended at 14:08

[redacted]

19th July 2021

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