Witness Name: Dr Edward Piper
Statement No.: First
Exhibits: EP/1 – EP/32
Dated: 11 December 2024

UK COVID-19 INQUIRY

WITNESS STATEMENT OF DR EDWARD PIPER

I, **DR EDWARD PIPER,** will say as follows:

1. I am Vice President, UK Medical & Scientific Affairs Director at AstraZeneca. In this role, I have responsibility for medical oversight of the AstraZeneca portfolio of medicines marketed in the UK. I am authorised by AstraZeneca to make this witness statement on its behalf. I have been asked to provide this witness statement as part of AstraZeneca's response to the UK Covid-19 Inquiry's Rule 9 Request for Evidence dated 27 September 2023 (the ***Rule 9 Request***) and the Inquiry's further requests for information received on 24 October 2024.

2. The matters covered in the Rule 9 Request are wide-ranging and extend beyond the knowledge of any one individual. In giving this statement, I am speaking on behalf of AstraZeneca as a whole and, in some places, I will refer to information provided to me from various sources and individuals. Unless stated otherwise, the facts and matters to which I refer in this witness statement are within my own knowledge and are true. Where the facts and matters to which I refer in this witness statement are not within my own knowledge, they are true to the best of my knowledge, information and belief. Where information has been provided to me by third parties, I identify the source of that information and believe it to be true.

3. While a draft witness statement was prepared by AstraZeneca's legal representatives based on discussions with me, I reviewed and amended that draft and ensured that that this statement is expressed in my own words, before signing the statement of truth below.

4. The documents I refer to for the purposes of providing the evidence in this witness statement are listed in the attached Annex 1 by the Unique Reference

Number (***URN***) attached to these documents by the Inquiry. When referring to a document in the body of this witness statement, I also cite the URN. I have worked with AstraZeneca's legal representatives to identify documents for inclusion in this way, having regard to the Inquiry's request to disclose key documents at this stage.

5. Nothing in this witness statement is intended to waive any privilege of AstraZeneca or any member of its corporate group, or any associated individual, and I am not authorised to, and do not, make any such waiver.

Content and structure of this statement

6. My statement is focused specifically on AstraZeneca's efforts to develop an effective therapeutic with a novel monoclonal antibody treatment, which culminated in a new medicine known as *Evusheld*. Where relevant, I cover the clinical trials and regulatory process, provide an overview of the interactions with the UK Government, and indicate any relevant innovations and lessons learned.

7. The structure of my statement is as follows:

   (a) **Section A:** Summary

   (b) **Section B**: What *Evusheld* is and how it works

   (c) **Section C**: AstraZeneca's efforts to develop an effective new therapeutic antibody for COVID-19

   (d) **Section D**: *Evusheld*: establishing manufacturing and supply chains

   (e) **Section E**: *Evusheld*: clinical trials

   (f) **Section F**: *Evusheld*: regulatory approvals

   (g) **Section G**: Interaction with the UK Government with respect to *Evusheld* and its potential procurement for the NHS

   (h) **Section H**: Future pandemic preparedness.

SECTION A: SUMMARY

8. From the earliest days of the pandemic, AstraZeneca was part of the global scientific effort to understand how to tackle and treat COVID-19 and we mobilised our research and development teams to focus on discovering new ways to do so.

9. Given our scientific expertise in infectious disease and proprietary antibody technology, one of the first things AstraZeneca did was to initiate a major programme of research to identify novel coronavirus-neutralising antibodies as a preventative or treatment approach to COVID-19. These are known as monoclonal antibodies or ***mAbs***.

10. mAbs are designed to boost the way the human immune system detects and kills viruses. In principle, mAbs can be given preventatively before exposure to the virus (pre-exposure prophylaxis or ***PrEP***), and also to treat and prevent disease progression in infected patients. These efforts culminated in the development of a combination long-acting antibody therapy, known as *Evusheld* (known internally as AZD7442 prior to approval, though I will generally refer to it throughout this statement as *Evusheld*).

11. The mAb development programme was a priority for AstraZeneca and we took steps to expedite this process. AstraZeneca ran many of the early-stage development processes in parallel to reduce the time it took to take the product forward to clinical trials.

12. The clinical trials produced results which demonstrated that *Evusheld* was efficacious both as a preventative (pre-exposure prophylactic) and as a treatment option for mild-to-moderate COVID-19. It was also well-tolerated with an overall positive benefit/risk profile.

13. AstraZeneca obtained global regulatory approvals for *Evusheld* in more than 30 countries, many of which then secured supplies of the product for deployment to patients including the United States, France, Japan and Australia.

14. A Conditional Marketing Authorisation (***CMA***) was granted in the UK for pre-exposure prophylaxis on 17 March 2022, and approval for treatment followed on 15 November 2022.

15. AstraZeneca discussed the potential procurement of *Evusheld* by the UK Government throughout the Inquiry's period of focus. Ultimately, the UK Government did not choose to procure *Evusheld* as part of its COVID-19 pandemic prevention or treatment response.

SECTION B: WHAT *EVUSHELD* IS AND HOW IT WORKS

16. *Evusheld* was designed to serve a critical need for patients at an increased risk of an inadequate immune response to a COVID-19 vaccine or for whom a COVID-19 vaccine would be unsuitable. We often refer to this patient population as "*immunocompromised*". Examples of immunocompromised people include those living with blood cancers, patients receiving chemotherapy, transplant patients, those on dialysis, people needing to take immunosuppressants or those who have a primary immune deficiency. It is estimated that between 2 to 4% of the general population is immunocompromised.

17. Immunocompromised patients remain at higher risk of severe outcomes, hospitalisation or death from COVID-19 even once vaccinated. [1] For example, one study showed that the immunocompromised made up a disproportionate number of COVID-related hospitalisations (21.9%), intensive care unit admissions (28.1%), and deaths (23.8%).[2]

18. *Evusheld* is a combination of two neutralising, human mAbs, tixagevimab (AZD8895) and cilgavimab (AZD1061), discovered by Vanderbilt University. The two mAbs in *Evusheld* bind to different areas of the SARS-CoV-2 spike protein. When an antibody binds to the SARS-CoV-2 spike protein, the virus is prevented from entering the body's cells to multiply. AstraZeneca decided to use both AZD8895 and AZD1061 together because of their combined potency at neutralising the SARS-CoV-2 virus and because they each bound to a distinct part of the spike protein of the virus.[3] AstraZeneca considered that the fact that each antibody bound to a different part of the virus's spike protein

[1] See Exhibit EP/1 - **INQ000420567** Rachael A. Evans et al, 'Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study' (2023) 35 The Lancet Regional Health - Europe.

[2] Ibid.

[3] See Exhibit EP/2 **INQ000521819** Jinhui Dong et al, 'Genetic and structural basis for recognition of SARS-CoV-2 variant neutralization by a two-antibody cocktail' (2021) Nature Microbiology 6, 1233-1244.

could help, insofar as possible, to account for future virus variants, on the basis that if a new variant knocked out the neutralising effect of one of the mAbs, the other mAb might still be available to neutralise the virus.

19. Figure 1 shows how the two antibodies in *Evusheld* operate to block the SARS-CoV-2 virus entering cells in the human body.

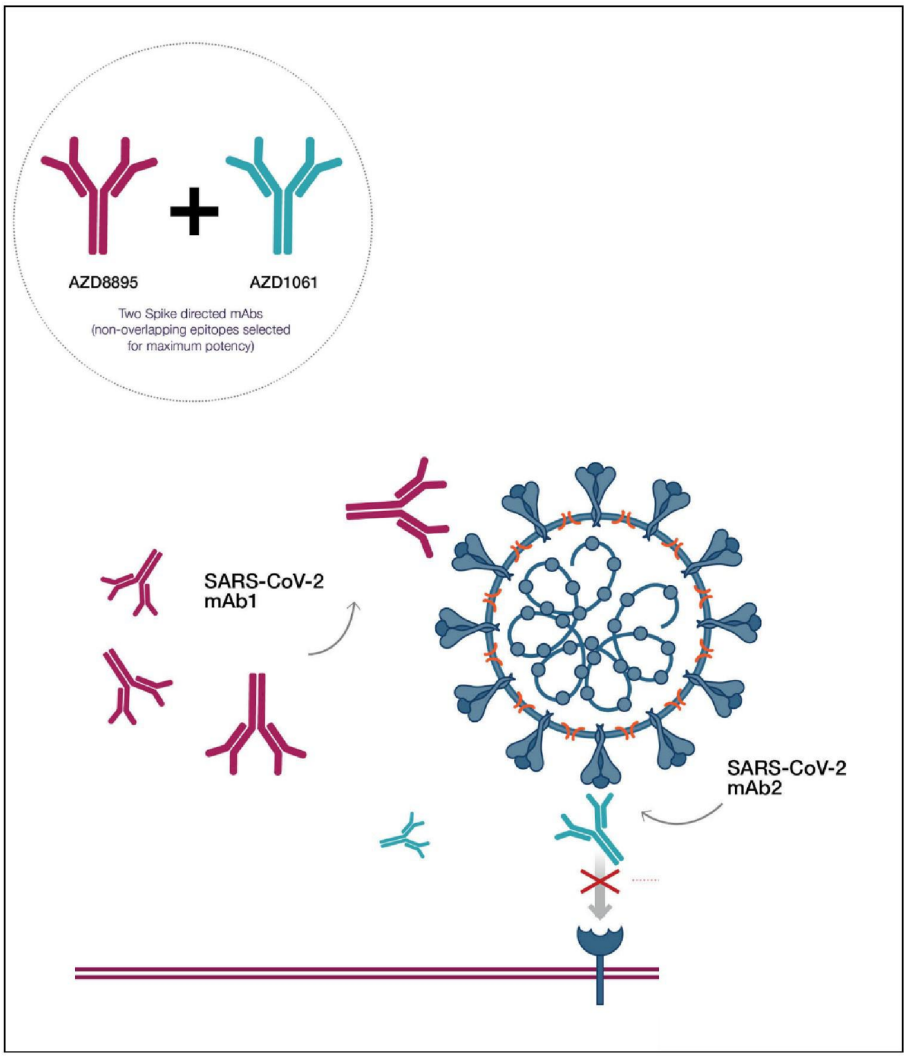

Figure 1: How Evusheld (AZD7442) blocks the SARS-CoV-2 virus from entering the body's cells

20. AstraZeneca applied its existing proprietary optimisation technology to the antibodies, including YTE™ modification to extend their half-lives.[4] This more

[4] A trio of amino acid mutations to the back end of each antibody – the Fc region – to extend its half-life. The YTE™ mutation prevents proteins known as Fc receptors from recognising the antibodies and removing them from circulation.

than tripled the longevity of their effectiveness. In other words, the use of this technology allowed *Evusheld* to provide longer-lasting protection against COVID-19 than would otherwise be possible (see Figure 2). Our optimisation technology also included applying a reduced Fc receptor binding which aims to minimise the theoretical risk of immunopathology (the risk of antibody-dependent enhancement of disease).

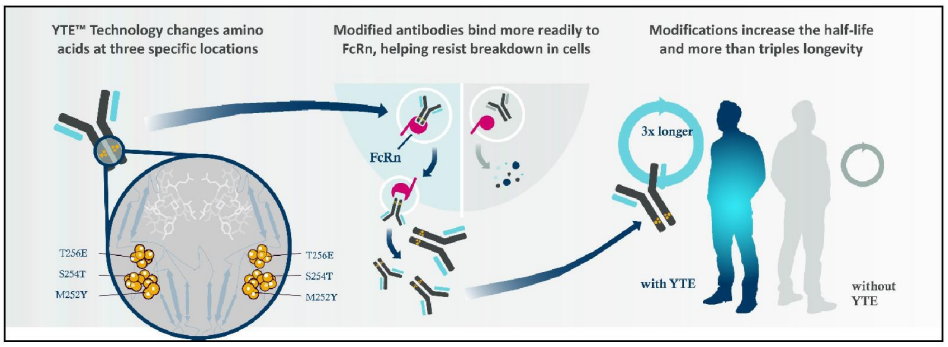

Figure 2: Use of AstraZeneca's proprietary technology to increase longevity

21. *Evusheld* can be delivered as an intravenous or intramuscular injection. It was the only available medicine in its class for the pre-exposure prevention of COVID-19 disease, when it was approved.

22. Although it was also approved for treatment of COVID-19 disease, *Evusheld* should not be confused with other medicines, such as antivirals, which are a different type of medicine that can be taken as a treatment option post-exposure to COVID-19.

SECTION C: ASTRAZENECA'S EFFORTS TO DEVELOP AN EFFECTIVE NEW THERAPEUTIC ANTIBODY FOR COVID-19

AstraZeneca's COVID-19 mAb programme

23. From early 2020, AstraZeneca began an accelerated programme to find an effective antibody for SARS-CoV-2 as a priority. The programme was supported by a wide range of global functions and individuals within AstraZeneca, all of whom were required to work together to design and deliver this complex product.

Antibody screening and investigation: process

24. Right from the outset, AstraZeneca expedited the screening of antibodies in-house and in collaboration with others. Three key sources were explored which could lead to a successful discovery and screening campaign:

    (a) Peripheral blood mononuclear cells samples from convalescing COVID-19 patients, i.e. patients who have recovered from COVID-19;

    (b) Immunised humanised mice; and

    (c) Laboratory techniques, e.g. phage display.

25. AstraZeneca's preferred option for antibody screening was to obtain antibodies from people who had recovered from the SARS-CoV-2 virus, whose immune systems have specifically generated antibodies to combat the virus.

26. Our scientists collaborated with academia and with public bodies and governments (in particular, the United States Defense Advanced Research Projects Agency (***DARPA***), with which AstraZeneca had an established relationship via prior pandemic preparedness work as part of DARPA's P3 Programme) to evaluate potential antibody candidates for future clinical use. The Chinese Academy of Sciences (China) and Vanderbilt University Medical Center (United States) also provided AstraZeneca with genetic sequences for antibodies they had discovered against SARS-CoV-2 for further in silico and in vitro assessment.

27. The objective of the screening process was to identify antibodies with the potential to bind to the spike protein of the SARS-CoV-2 virus, and for their neutralising potency. AstraZeneca screened billions of B cells which make antibodies and by June 2020, AstraZeneca had further evaluated over 1,500 antibodies which bound to the spike protein. Potency evaluation involved in vitro tests using pseudo virus (i.e. not live SARS-CoV-2 virus), and promising antibody candidates underwent a further pre-clinical safety and efficacy assessment, including using live virus, for which AstraZeneca collaborated with the United States Army Medical Research Institute of Infectious Diseases and the University of Maryland School of Medicine.

28. Of the 1,500 spike-binding antibodies identified, 25 were confirmed to be highly potent and were investigated more deeply. 10 were taken further through

AstraZeneca's development process, including applying and evaluating the effect of the optimisation techniques I have described above, and evaluating where exactly they bound to the virus spike protein.

29. The two antibodies which were combined to create *Evusheld* were identified by and licensed from Vanderbilt University. Individually, these mAbs were effective in binding to and neutralising SARS-CoV-2 virus and the combined results of these two mAbs used together were particularly promising.

30. Figure 3 below demonstrates the speed of the *Evusheld* development process. AstraZeneca ran many processes which would usually be run sequentially in parallel, and advanced multiple antibody candidates through our development process (usually we would only take one or two through the process, given the resources required to do so). Ultimately, AstraZeneca managed to cut the identification and early development process down to 7.5 months.

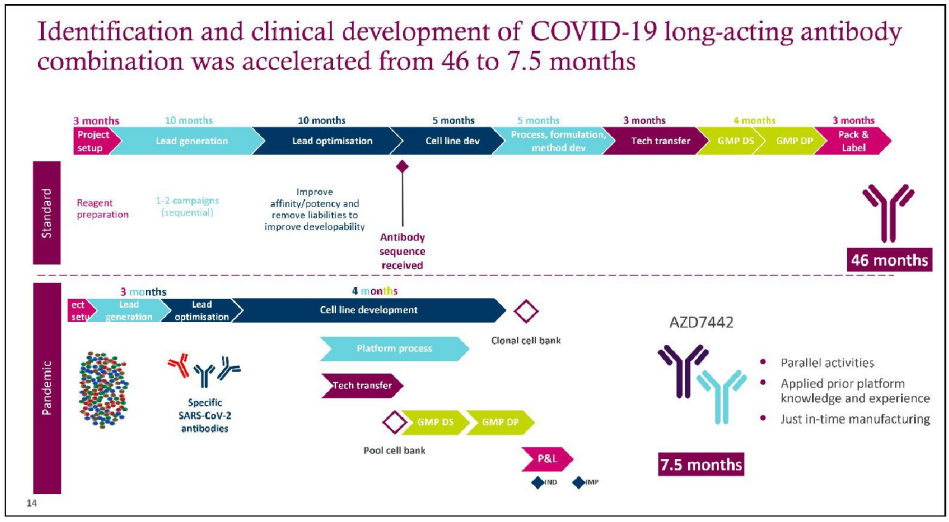

Figure 3: Development of Evusheld on an accelerated timeline

SECTION D: *EVUSHELD*: ESTABLISHING MANUFACTURING AND SUPPLY CHAINS

31. *Evusheld* is a biologic medicine. Biologics have large and complex structures, which means that they can only be replicated by a biological process using living cells or organisms.

32. AstraZeneca manufactured clinical supply for *Evusheld* in-house at our Gaithersburg Pilot Facility in the United States. AstraZeneca ran processes to ensure scaled-up commercial supply in parallel with ongoing development

activities which would, again, usually be carried out sequentially, as demonstrated by Figure 3 above. For commercial supply, AstraZeneca needed to work with third party contract manufacturing organisations (***CMOs***).

33. As biological manufacturing is a specialised and sophisticated process, the number of CMOs and manufacturing sites with the capability to produce these medicines is limited. This is because the manufacturing process is highly specialised in terms of facilities, equipment, qualified staff, and the complexity of the technology transfer processes.[5] The volumes of antibody per litre of bioreactor capacity required for commercial mAb supply are also generally much greater than, for example, vaccines. This, combined with the complexity of the manufacture process, also makes mAb production much more expensive than for many other medicines.

34. The COVID-19 pandemic itself made it more difficult to establish the requisite manufacturing capacity. This was for a number of reasons, including impact on staffing, physical restrictions and controls and increased worldwide demand for manufacturing capacity and materials. AstraZeneca ultimately secured manufacturing capacity with three experienced CMOs for the global supply of *Evusheld*. These were Lonza in the United States, Samsung Biologics in South Korea, and WuXi Biologics in China, all of which AstraZeneca had worked with previously.

35. For *Evusheld*, wherever possible, AstraZeneca sought to streamline the manufacturing process. For example, AstraZeneca deployed tried and tested platform technology, and kept processes as simple as possible. This helped to reduce the technology transfer time to our CMOs. Certain aspects of our yield optimisation processes were also deferred, which would usually be deployed as an iterative part of the development process to optimise production performance. AstraZeneca had to accept that this might mean overall lower yields, but in the context of the pandemic AstraZeneca believed that this was the right thing to do to ensure that commercial supply would be ready as soon as possible.

[5] The process of transferring the technology and manufacturing process know-how to enable CMOs to manufacture the product at their own facilities.

SECTION E: *EVUSHELD*: CLINICAL TRIALS

Phase I trial

36. In August 2020, the first patients received *Evusheld* in a Phase I trial called NCT04507256. The trial took place in the UK at University College Hospital, London and was designed to assess the safety and tolerability of *Evusheld* in healthy adults. It was funded by DARPA and the Biomedical Advanced Research and Development Authority[6] (***BARDA***), part of the United States Government.

37. Results of the Phase I trial suggested that *Evusheld* was well-tolerated in healthy adults. Pharmacokinetic[7] analyses suggested *Evusheld* could offer protection of six months or more against symptomatic COVID-19. Therefore, AstraZeneca decided to progress to larger late-stage Phase III trials to further evaluate its safety and efficacy as a potential preventative and treatment option against COVID-19.

Phase III trials: overview

38. AstraZeneca ran three clinical Phase III trials for *Evusheld*: PROVENT, TACKLE and STORMCHASER which were funded in part by BARDA. These trials were all randomised, double-blind, placebo-controlled and multi-centre. They were designed to assess the safety and efficacy of *Evusheld* against different primary endpoints in clinically vulnerable patient communities.[8]

39. In short, these Phase III trials demonstrated that *Evusheld* was efficacious in pre-exposure prophylaxis in people not currently infected with SARS-CoV-2 and also in the treatment of people already infected with SARS-CoV-2 to reduce the risk of progression to severe illness. In terms of safety, all the studies showed that *Evusheld* was well-tolerated with an overall positive benefit/risk profile.

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[6] Part of the Office of the Assistant Secretary for Preparedness and Response at the United States Department of Health and Human Services.

[7] Evidence of a drug's absorption, bioavailability, distribution, metabolism and excretion.

[8] Although the participant population was broader.

***Evusheld*: Phase III trial: PROVENT**

40. The PROVENT trial began in November 2020. It was a pre-exposure prophylaxis trial designed to assess *Evusheld* for the prevention of COVID-19 in participants who were not infected at baseline. Approximately 43% of participants were 60 years and over, and more than 75% had baseline co-morbidities and other characteristics that are associated with an increased risk for severe COVID-19 should they become infected.

41. AstraZeneca announced first results from the trial in August 2021. These results showed that *Evusheld* reduced the risk of developing symptomatic COVID-19 by 77% compared to placebo. AstraZeneca reported the six-month follow-up assessment in November 2021. The results were compelling, showing an 83% reduction in high-risk patients getting any symptom of COVID-19.

42. The PROVENT results were subsequently published in the New England Journal of Medicine.[9]

***Evusheld*: Phase III trial: TACKLE**

43. The TACKLE trial began in January 2021. It was designed to assess *Evusheld* for the outpatient treatment of mild-to-moderate symptomatic COVID-19 patients in preventing progression to severe COVID-19 or death. 90% of participants had baseline co-morbidities and other characteristics that put them at high risk of progression to severe COVID-19.

44. AstraZeneca reported the primary analysis on 11 October 2021. The results were positive, showing the risk of developing severe COVID-19 or death (from any cause) was reduced by 50% compared to placebo. In patients who received treatment within five and three days of symptom onset, the reduction was 67% and 88%, respectively.

45. Peer-reviewed results were published in the *Lancet* on 2 June 2022.[10]

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[9] See Exhibit EP/3 **INQ000521825** M.J. Levin et al, 'Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19' (2022) NEJM 386.

[10] See Exhibit EP/4 **INQ000521826** Hugh Montgomery et al, 'Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial' (2022) 10 The Lancet Respiratory Medicine, 985-996.

Evusheld: Phase III trial: STORMCHASER

46. In addition, we ran the STORMCHASER PHASE III trial, which began in December 2020. It was designed to assess *Evusheld* for the prevention of symptomatic COVID-19 in recently exposed participants (i.e. post-exposure prophylaxis) and was targeted at high risk environments for infection.

47. In June 2021, AstraZeneca announced the results of the trial. Although *Evusheld* reduced the risk of developing symptomatic COVID-19 by 33% compared to placebo, this was not statistically significant and so STORMCHASER did not meet its primary endpoint. AstraZeneca realised as part of this trial that very early intervention was critical in order to be able to avoid any COVID-19 symptoms at all. For example, *Evusheld* was more effective among patients who had tested positive but had no notable symptoms (i.e. patients who were very early on into infection), and reduced the risk of developing symptomatic COVID-19 by 73% compared with placebo.

SECTION F: *EVUSHELD*: REGULATORY APPROVALS

Introduction

48. Following the announcement of positive high-level results from the PROVENT pre-exposure prophylaxis Phase III trial in August 2021, AstraZeneca began seeking regulatory approvals for *Evusheld* globally.

49. AstraZeneca's first submission was made in the United States in September 2021, with further dossiers submitted worldwide thereafter. Regulatory approvals followed, including in Australia, the United States, the UK and the European Union. In total, *Evusheld* received regulatory approval in more than 30 countries around the world.

UK regulatory approval

50. With respect to the regulatory approval process with the UK's Medicines and Healthcare products Regulatory Agency (***MHRA***), I understand from my regulatory colleagues that the MHRA was responsive and helpful throughout the process.

51. The MHRA engaged in constructive early pre-submission meetings and responded to communications and reviewed documents quickly. As part of this

dialogue, AstraZeneca asked the MHRA whether we might be able to make use of the Early Access to Medicines Scheme, which can be used to provide early access for patients with life threatening or debilitating conditions. The MHRA provided a clear view that the appropriate regulatory pathway for *Evusheld* would be to apply for a CMA on a full dossier basis.

52. To ensure an expedited review, the MHRA agreed to allow AstraZeneca to make submissions by email or via electronic file sharing, which made the submission process more efficient. The MHRA also agreed to review regulatory submissions for *Evusheld* on an accelerated rolling review basis. This meant that it reviewed the data provided to it as soon as the data became available and provided its questions and feedback on a rolling basis with quick turnaround times for the analysis of our responses. As a result, it took six weeks from the point of submission of our regulatory dossier at the end of January 2022 to the granting of a CMA for *Evusheld* for PrEP on 17 March 2022.

53. *Evusheld* was approved for the prevention (pre-exposure prophylaxis) of COVID-19 in adults who were unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination was not recommended.[11,12]

54. In November 2022, the authorisation was extended to include post-exposure treatment of COVID-19, for adults at risk of progressing to severe COVID-19. This followed the further results from the TACKLE Phase III trial. AstraZeneca similarly found that the MHRA reviewed this submission on an expedited basis.

Current status

55. *Evusheld* remains approved for pre-exposure prophylaxis and for treatment of mild to moderate COVID-19 in many countries, including in the European Union, Japan and the UK.[13] Although *Evusheld* remains available for use in those markets in which it is approved, current commercial use is very low. More

[11] See Exhibit EP/5 **INQ000397431** MHRA, Public Assessment Report 'EVUSHELD 150mg / 150 mg solution for injection tixagevimab, cilgavimab' (2022) PLGB 17901/0360.

[12] See Exhibit EP/6 **INQ000397432**, MHRA, 'Summary of Product Characteristics for *Evusheld*', (*MHRA*, 15 November 2022).

[13] As at 7 November 2024.

recently, due to a lack of commercial demand, AstraZeneca has withdrawn or not renewed approvals in a number of markets.[14]

SECTION G: INTERACTION WITH THE UK GOVERNMENT WITH RESPECT TO *EVUSHELD* AND ITS POTENTIAL PROCUREMENT FOR THE NHS

Introduction

56. AstraZeneca had many interactions with the UK Government (including with Ministers, COVID-19 taskforces and advisors) around *Evusheld* and its potential procurement throughout the Inquiry's period of focus.

57. AstraZeneca's dialogue with the UK Government covered topics such as the clinical data, the progress of the regulatory submission to MHRA, and the potential numbers of immunocompromised people in the UK who needed a pre-exposure preventative alternative to vaccination. In particular, the AstraZeneca team continued to evaluate the binding capability as well as the neutralising potency of *Evusheld* versus emerging variants post-MHRA authorisation and discussed this with the UK Government.[15] AstraZeneca supplied additional information and confirmatory data, including pharmacokinetic evidence and ongoing viral neutralisation data against emerging variants of concern.

58. From mid-2021, AstraZeneca also worked with the UK Health Security Agency (***UKHSA***) and its laboratories in Porton Down to assess the neutralisation ability of *Evusheld*, which enabled the rapid generation of in-vitro neutralisation data to inform an initial view on the potential for Evusheld to be clinically effective as the virus continued to evolve. As I describe below, the results from Porton Down were provided in May 2022.

59. I understand that the Inquiry is also interested in the work of RAPID C-19. We understood that RAPID C-19 had been established to advise and assist the UK Government in horizon scanning for medicines to combat COVID-19. However, AstraZeneca's own interactions with members of RAPID C-19 were very limited. From time-to-time, UK Government advisors (for example, Professor

[14] In addition, the US suspended its emergency use authorisation in 2023 based on its assessment of neutralisation rates in respect of then prevalent variants in the United States.

[15] See Exhibit EP/7 **INQ000521830** Wanwisa Dejnirattisai et al, 'SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses' (2022) Cell 185, 467-484.

Andrew Owen – see below) joined occasional meetings with the TTF/ATTF but beyond this, interaction was sparse.

60. In the sections below, I provide a brief chronological account of some of AstraZeneca's key interactions with the UK Government based on discussions and input from my colleagues. My direct involvement in these discussions was that I was involved in some of those which were more scientific in nature and I have tried to indicate instances below where I was directly involved in meetings. I did not have direct involvement with such discussions until January 2022 when I started my current role.

Overview of the dialogue with the UK Government around the potential procurement of *Evusheld* via emergency means

61. From the very early stages of the pandemic, AstraZeneca and the UK Government discussed mAbs' potential to form an important part of the response to COVID-19 for immunocompromised patients.

62. Until autumn 2021, AstraZeneca's primary point of contact with respect to the potential procurement of *Evusheld* was the Vaccines Task Force (***VTF***).[16,17] Our experience of dealing with the VTF regarding the potential for an effective mAb was positive, and as I explain further below, it is my belief that the VTF was an appropriate body to consider *Evusheld*'s prophylactic potential alongside other options for prophylaxis, including COVID-19 vaccines.

63. In the early stages, discussions were led on the AstraZeneca side by Sir Mene Pangalos (then our Executive Vice President, Biopharmaceuticals R&D). Tom Keith-Roach (President, AstraZeneca UK) took on a lead role from AstraZeneca UK, with respect to key UK Government interactions concerning *Evusheld* from early 2021.

64. The UK Government formally indicated early on that it was interested in securing advance supply of *Evusheld* on an expedited basis, if *Evusheld*

[16] Our key contacts within the VTF included Madelaine McTernan (then Director UKGI), Nick Elliott (then DG VTF SRO), and Joanne Scott (then Senior Commercial Officer in the VTF).

[17] We also had dialogue with other UK Government stakeholders including Lord Bethell (then Parliamentary Undersecretary for Innovation within the Department for Health and Social Care) and Matt Hancock (then Secretary of State for Health and Social Care).

received regulatory approval. In the second half of 2020, senior Ministers stated this intent publicly.[18] Discussions continued intermittently until around December 2020 while, at the same time, other international governments also looked to secure their own supplies.

65. In December 2020, when it had become clear that the UK would soon be able to commence a national COVID-19 vaccination programme for the general population, the VTF told AstraZeneca that, in light of the vaccination programme, they considered there was less demand for prophylactic antibodies, though they were still interested in exploring the possibility of procuring Evusheld in smaller volumes (in the order of tens of thousands).

66. From 2021 onwards, while intermittent discussions with the UK Government concerning possible procurement of *Evusheld* continued, smaller volumes were under consideration and there generally appeared to be less interest from the UK Government in procurement.

67. From Autumn 2021, the Therapeutics Taskforce (***TTF***) took over the lead responsibility for discussions concerning potential procurement of *Evusheld* from the VTF. It was confirmed to us that there had been a reorganisation within the UK Government – the VTF was to focus solely on COVID-19 vaccines and responsibility for *Evusheld* transitioned to the TTF. The TTF later amalgamated with the Antivirals Taskforce in April 2022 and became known as the ATTF.

68. The TTF/ATTF had a wide remit which included therapeutic treatment options such as antivirals as well as prophylactic mAbs. The TTF/ATTF was under the responsibility of the Department of Health and Social Care (***DHSC***) in contrast to the VTF, which had been under the direction of the Department for Business, Energy & Industrial Strategy. Our primary contact point within the TTF/ATTF was Charlotte Taylor (Acting Director of the TTF/ATTF).

69. Although AstraZeneca interacted frequently with the TTF/ATTF, from our perspective there was no regular meeting cadence in place with the TTF/ATTF and meetings and discussions were sporadic and ad hoc. In hindsight, AstraZeneca was not clear on the process the TTF/ATTF was following to govern the potential procurement of *Evusheld*. For example, neither a

[18] See Exhibit EP/8 - **INQ000397430** Letter from Alok Sharma MP to Greg Clark MP (23 July 2020).

timeframe nor specific decision-making criteria existed (as far as AstraZeneca knew).

70. There were some periods, after the initial period in 2020 and before the time when we learned that the UK Government would not be procuring *Evusheld* by emergency means (see below), where discussions with the UK Government intensified and became more focussed. In particular, these were:

(a) in September 2021, once the PROVENT primary results became available;

(b) in late November 2021, when the UK Government was taking steps to address increasing case numbers and the emergence of new Omicron variants; and

(c) shortly before and after we achieved UK marketing approval in March 2022.

71. In August 2021, we announced the PROVENT Phase III results. There followed a number of meetings where we presented the PROVENT results and discussed potential procurement with the UK Government.[19] In October 2021, the results from the TACKLE Phase III trial were released and we updated the TTF/ATTF.

72. At the end of November 2021, the TTF/ATTF contacted AstraZeneca to ask about the potential timing of supply. We responded that, at that time, we could commit to a supply of 50,000 doses with deliveries to be split between December 2021 and April 2022, noting that this would be subject to being able to enter into a firm contract soon, given that global supply allocation was a live and dynamic issue. Although further discussions followed about potential supply and while we provided further clinical data, these did not lead to any firm commitment by DHSC.

73. In January 2022, AstraZeneca met (via the TTF/ATTF) Professor Andrew Owen, Professor of pharmacology and therapeutics at the University of

[19] For example, in September and October 2021, there were a number of meetings and communications with the TTF/ATTF and we also met with Matt Hancock, Nadhim Zahawi (then Parliamentary Under-Secretary of State at the DHSC), and Sajid Javid (then Secretary of State Secretary of State for Health and Social Care).

Liverpool, who we understood from the TTF/ATTF had been commissioned by RAPID C-19 to advise the Chief Medical Officer in respect of *Evusheld* pharmacokinetic data. Professor Owen had concerns about *Evusheld*'s potency and efficacy against Omicron variants. Professor Owen was concerned about the anatomical compartmental penetration and dose assumptions and the projected potency against Omicron BA. 2 based on live virus assays, which showed some fold changes in in-vitro data. He assumed fold changes meant that the product may have been less effective.

74. We had the opposite view and were convinced that, despite fold changes, the product maintained its effectiveness. We sent follow-up data detailing the evidence supporting retained efficacy to the TTF after the meeting and there was also a follow-up meeting with Professor Owen.

75. AstraZeneca did take into account dosage concerns expressed by Professor Owen and took the precautionary step of indicating in our PrEP CMA that a higher 600mg dose may be more appropriate for certain variants, including Omicron BA.1 and Omicron BA.1.1. As noted below, we offered a 600mg dose for PrEP to the UK Government in July 2022 as part of our at-risk offer for supply over the winter.[20]

76. CMA for *Evusheld* in a PrEP indication was granted by the MHRA on 17 March 2022 and, shortly afterwards, we also announced independent live virus studies which had demonstrated that *Evusheld* retained its potent neutralising activity against emerging Omicron variants of concern. Around this time, we again sought clarity as to the path ahead for the procurement of *Evusheld*. For example, in March we wrote to Sajid Javid, then Secretary of State for Health and Social Care[21] and to Jeremy Hunt (then Chair of the House of Commons Health Select Committee). There was also some communication around this time (in April and May) with the Chief Medical Officer, Chris Whitty.

77. In April 2022, Sir Mene Pangalos wrote to Chris Whitty and to Patrick Vallance (then Chief Scientific Advisor). He stated that AstraZeneca had already supplied a wealth of evidence to the ATTF confirming the neutralisation which

[20] This remained in line with our existing MHRA PrEP approval. We note that the standard recommended dose for treatment is 600mg per the subsequent MHRA approval for the treatment indication.

[21] Cc. TTF/ATTF.

Evusheld was achieving and he sought a way to resolve any issues which remained. In a response dated 20 April 2022 (which he described as the "*collective current view*"), Chris Whitty expressed the need for "*confidence in the efficacy and duration of protection against the currently dominant variant*", noting the speed of COVID-19 variants and that in vitro data had shown reduced efficacy of *Evusheld* against some variants, including Omicron. He referred to the ongoing confirmatory work with Porton Down. [22] Sir Mene replied that his key concern was the time it was taking for decision-making to happen in comparison to other countries, noting a delay in receiving the Porton Down analysis. He welcomed clarity as to the overall decision-making process and as to who was the ultimate decision-maker in respect of *Evusheld.* [23]

78. At the end of April, we received an update from the TTF/ATTF that it was continuing to work at pace on outstanding workstreams, although acknowledging that there had been some delays with UKHSA live virus testing at Porton Down.

79. There was a follow-up meeting in May 2022 with Chris Whitty and others, including a representative from the TTF/ATTF, and AstraZeneca representatives including Sir Mene Pangalos. During this meeting, we attempted to allay the concerns which the Chief Medical Officer had expressed in his earlier correspondence concerning efficacy against Omicron variants, including with reference to the independent live virus studies (which we had announced on 21 March 2022). We explained that we believed that *Evusheld* would retain its ability to neutralise against emerging variant strains, including BA.4 and BA.5, and noted that virus neutralisation data was expected to be available soon. We followed up to provide Chris Whitty and the ATTF with this data,[24] which we also published in a press release on 25 May 2022.

80. On 16 May 2022, AstraZeneca received the analysis of *Evusheld* conducted by Porton Down. This demonstrated *Evusheld*'s effectiveness against prevalent sub-variants at that time. On 25 May 2022, AstraZeneca wrote to Sajid Javid

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[22] See Exhibit EP/9 - **INQ000521823** Letter from DHSC (Chris Whitty) to AstraZeneca – 20 April 2022.

[23] See Exhibit EP/10 - **INQ000521817** Emails between AstraZeneca and DHSC – 1 to 22 April 2022.

[24] See Exhibit EP/11 **INQ000521814** Email from AstraZeneca to ATTF/TTF (Charlotte Taylor) – 25 May 2022 and Exhibit EP/12 - **INQ000521810** Attachment to email from AstraZeneca to ATTF/TTF (Charlotte Taylor) – 25 May 2022.

(then Secretary of State for Health and Social Care)[25] referencing the results of the Porton Down analysis of *Evusheld*. We explained that, in view of the importance the UK Government had previously placed on the UKHSA testing in the procurement process, we were therefore seeking confirmation that this data now enabled the UK Government to confirm suitable effectiveness and that it had addressed any outstanding questions. If not, we requested clarity on how the results were being analysed by the UK Government.[26]

UK Government decision not to procure by emergency routes

81. In May 2022, AstraZeneca learned that the UK Government planned to issue a "Dear Colleagues" letter to Parliament which indicated that it did not intend to procure *Evusheld* via emergency routes, on the basis of its concerns about efficacy against newer COVID-19 variants. AstraZeneca was informed of this intention by Sajid Javid's team by telephone on 18th May 2022. The TTF/ATTF communicated this in parallel by telephone to Tom Keith-Roach and extracts of a draft of the "Dear Colleagues" letter were provided to AstraZeneca by email. The draft letter which AstraZeneca saw at that time explained that, in the UK Government's view, *Evusheld*'s clinical effectiveness against Omicron variants, such as BA.2 and BA.4 and BA.5, needed further assessment and the results of UKHSA live virus laboratory tests needed careful consideration and expert review.[27]

82. AstraZeneca disagreed strongly with the basis of the conclusions in the draft letter, and stood by the data which showed *Evusheld* was still neutralising effectively at that time. AstraZeneca set out its position in a letter to the TTF/ATTF and to the Secretary of State. We referenced recent data confirming the effectiveness of *Evusheld* against prevalent variants, including the Porton Down testing carried out on behalf of UKHSA, which we explained was consistent with results obtained from analysis from other sources.[28] AstraZeneca was subsequently informed by the TTF/ATTF on 23 May 2022 that it was very unlikely that the UK Government would issue the "Dear

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[25] Copied to the TTF/ATTF and Chris Whitty.

[26] See Exhibit EP/13 **INQ000521809** Letter from AstraZeneca to Sajid Javid MP – 25 May 2022.

[27] See Exhibit EP/14 **INQ000521818** Emails between AstraZeneca and TTF/ATTF – 20 to 23 May 2022.

[28] See Exhibit EP/13 **INQ000521809** Letter from AstraZeneca to Sajid Javid MP – 25 May 2022 and Exhibit EP/14 **INQ000521818** Emails between AstraZeneca and TTF/ATTF – 20 to 23 May 2022.

Colleagues" letter so close to the Parliamentary recess.[29] No such letter was, to AstraZeneca's knowledge, issued at that time.

83. We were keen to try to see whether there was still a way *Evusheld* could be made available over the winter and, in July 2022, AstraZeneca set out formal proposals to the UK Government to supply *Evusheld* to protect the highest-risk immunocompromised sub-groups over the winter on an innovative, outcome-based risk-sharing basis.[30] There was a meeting on 4 July with Sajid Javid, who expressed interest in such a proposal, and the formal proposal was presented in a letter on 13 July 2022 to Stephen Barclay (who had succeeded Sajid Javid in the intervening days since that meeting) from Sir Mene Pangalos and Tom Keith-Roach on behalf of AstraZeneca.[31,32]

84. AstraZeneca's proposal was to provide a double dose of *Evusheld* at the price previously proposed for the single dose to address questions which the UK Government had raised around efficacy against Omicron. We also offered to refund 100% for any patient hospitalised due to COVID-19 or infected and treated in the community with an antibody or mAb, and to defer a portion of the contract value to recognise that payment would be conditional upon successful outcomes.

85. At that time, AstraZeneca remained confident in *Evusheld*, and felt that such a risk-sharing approach might address the UK Government's concerns around new variants. We said when making this offer that we expected that an assessment by the National Institute for Health and Care Excellence (***NICE***) could be completed by the time patients required a second dose, in order to inform a decision on longer-term access to *Evusheld*.

86. Many UK clinicians and those representing immunocompromised groups had been requesting that the UK Government procure *Evusheld* for the NHS for

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[29] See Exhibit EP/14 - **INQ000521818** Emails between AstraZeneca and TTF/ATTF – 20 to 23 May 2022.

[30] We had already discussed a willingness at a high level to explore possibilities to de-risk the UK Government's procurement of *Evusheld* with the TTF/ATTF before, for example via potential rebate mechanisms of the cost of treatment.

[31] Copied to the TTF/ATTF and Chris Whitty.

[32] See Exhibit EP/15 - **INQ000521822** Letter from AstraZeneca to Stephen Barclay MP – 13 July 2022 and Exhibit EP/16 - **INQ000521806** Appendix to letter from AstraZeneca to Stephen Barclay MP – 13 July 2022.

some time. In July 2022, a clinical consensus statement was published by over 120 clinicians representing 17 different clinical specialities from across all four devolved nations (on behalf of the All-Party Parliamentary Group on Vulnerable Groups to Pandemics). This stated that pre-exposure prophylaxis would have clinical benefit to immunocompromised people, and that a protective antibody treatment programme should be delivered as soon as possible.[33] That same month, charity groups also wrote to urge the UK Government to procure prophylactic mAb therapies such as *Evusheld*.[34]

87. AstraZeneca's risk-sharing proposal as set out in our letter of 13 July 2022 was not accepted. In August 2022, the UK Government confirmed its decision not to procure *Evusheld* on the basis that it still had concerns about its clinical effectiveness against then prevalent variants.

88. On 9 August 2022, Stephen Barclay, by then Secretary of State for Health and Social Care, wrote a letter to Sir Mene Pangalos and Tom Keith-Roach.[35] He said that, while the value of our proposal was recognised, there remained questions from the UK Government about "*the extent to which laboratory testing confirms the level of in vivo neutralisation against recent prevalent Omicron subvariants and therefore the clinical effectiveness of Evusheld*." Mr Barclay stated that the decision had been based on independent clinical advice, including from RAPID C-19, and that the Chief Medical Officer was in agreement that *Evusheld* should now be referred for evaluation to NICE for NHS procurement.[36]

89. On the same day (9 August 2022), the ATTF/TTF communicated to us that there would also be wider communications with stakeholders, including Parliamentarians, via a new "Dear Colleagues" letter and shared a near final draft of that letter with AstraZeneca (which was similar to the draft shared back

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[33] See Exhibit EP/17 - **INQ000397433** All-Party Parliamentary Group on Vulnerable Groups to Pandemic, 'National Clinical Expert Consensus Statement' – 27 July 2022.

[34] See Exhibit EP/18 - **INQ000397429** Letter from charities and groups representing patients who remain vulnerable to Covid to Stephen Barclay MP – 23 August 2022.

[35] See Exhibit EP/19 - **INQ000499889** Letter from Stephen Barclay MP to AstraZeneca – 9 August 2022.

[36] The UK Government also suggested that AstraZeneca explore the possibility of including *Evusheld* in the PROTECT-V study, a multi-product prophylaxis study. AstraZeneca did consider this, but ultimately did not proceed with it.

in May 2022).[37] The draft "Dear Colleagues" letter said that the there was "*a lack of available data [on Evusheld] particularly around dosage and efficacy against the Omicron variant*", and so *Evusheld* would not be made available through emergency routes. Instead, it was noted, the UK Government intended to refer *Evusheld* to NICE in accordance with the advice of the Chief Medical Officer and RAPID C-19.

90. On 10 August 2022, AstraZeneca responded to Stephen Barclay[38] expressing our disappointment in the UK Government's decision not to accept our proposal to make *Evusheld* available to NHS patients that winter. We explained that we were surprised that the recommendation to the Secretary of State and the Chief Medical Officer had been that more evidence of effectiveness against new Omicron variants was required. We said that, in our view, there was a significant body of real-world evidence (***RWE***) derived from other countries where *Evusheld* had been deployed, which continued to demonstrate efficacy in reducing symptomatic and severe disease. We asked for the opportunity to meet UK Government advisors to discuss their views to see whether we could overcome their concerns, noting that there had been limited opportunity to engage with them through the ATTF. We said that, while we would submit for a NICE appraisal, we did not anticipate that this process would be completed until summer 2023.[39]

91. On 12 August 2022, the UK media reported that the UK Government would not be purchasing Evusheld and that a review by NICE would follow. A Statement at that time from the Department of Health to the BBC reported that "*following a robust review of the available data [our] clinical experts advise there is currently insufficient data on the duration of protection offered by Evusheld in relation to the Omicron variant and the government will not be procuring any doses at this time.*" AstraZeneca was surprised by this public development, since it considered there was still an ongoing dialogue with the UK Government around potential procurement.

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[37] See Exhibit EP/20 - **INQ000521816** Email from TTF/ATTF (Charlotte Taylor) to AstraZeneca – 9 August 2022 and Exhibit EP/21 **INQ000521811** Attachment to email from TTF/ATTF (Charlotte Taylor) to AstraZeneca – 9 August 2022.

[38] Including a copy to the Chief Medical Officer and the TTF/ATTF.

[39] See Exhibit EP/22 - **INQ000521821** Letter from AstraZeneca to Stephen Barclay MP – 10 August 2022.

92. There was a meeting which I attended with Stephen Barclay, Charlotte Taylor and others, including Lucy Chappell (Chief Scientific Adviser for the DHSC) on 18 August 2022. My overall impression was that the Secretary of State's intention remained to issue a "Dear Colleagues" letter after the summer recess (due to end in early September 2022) and that the decision not to procure by emergency means was unlikely to change, although we were informed that UK Government experts were due to look at the RWE again.

93. There was a follow-up meeting which I attended with Charlotte Taylor, Lucy Chappell and others (including representatives from NICE) on 26 August 2022 to discuss in detail key RWE supporting *Evusheld* effectiveness, as well as in-vitro data supporting the RWE effectiveness observations. From the AstraZeneca side, this was led by clinical / technical personnel, including me.[40] We outlined the robust evidence that demonstrated continued effectiveness against variants of concern. We discussed in particular the following RWE:

(a) The clinical RWE from two key US-based real-world studies[41], executed during the BA.1 / BA. 1.1 / BA. 2 surges using 600mg doses; and

[40] RWE meeting with AstraZeneca dated 26 August 2022.

[41] See Exhibit EP/23 - **INQ000521805** Al Jurdi A et al., 'Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the Omicron wave' (2022) Am J Transplant, 3130-3136 and Exhibit EP/24 - **INQ000521832** Young-Xu et al., 'Tixagevimab/cilgavimab for prevention of COVID-19 during the Omicron surge: retrospective analysis of national veterans affairs electronic data' (2022) medRxiv.

(b) Clinical evidence from real-world settings, including France[42], Israel[43], and the US[44], conducted during BA.1 / BA. 1.1 / BA. 2 surges using a 300mg dose.

94. Ultimately, the UK Government's decision did not change, and *Evusheld* was referred to NICE for appraisal in August (see below).

95. The UK Government's decision was met with great disappointment by members of the immunocompromised community and relevant charities, who were reported to consider that *Evusheld* could fulfil a critical unmet need at that time.

96. On 6 October 2022, RAPID C-19 published a report summarising the recommendations it had made to the Chief Medical Officer following a review of *Evusheld* for pre-exposure prophylaxis. The report indicated that in May 2022 it had advised the Chief Medical Officer that the non-clinical data it had analysed concerning efficacy against Omicron variants suggested that it did not warrant action to progress toward patient access. The report explained that subsequent review by RAPID C-19 of RWE had led it to conclude that the quality of data was insufficient to warrant action to progress to patient access before the completion of NICE's technological appraisal, and that it considered

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[42] See Exhibit EP/25 - **INQ000521813** Bruel T et al, 'Serum Neutralization of SARS-CoV-2 Omicron Sublineages BA.1 and BA.2 in Patients Receiving Monoclonal Antibodies' (2022) Nature Medicine and Exhibit EP/26 **INQ000521812**, Bertrand D et al, 'Efficacy of Anti-SARS-CoV-2 Monoclonal Antibody Prophylaxis and Vaccination on the Omicron Variant of COVID-19 in Kidney Transplant Recipients' (2022) Kidney International.

[43] See Exhibit EP/27 **INQ000521808**, AstraZeneca, 'An Observational Study to Assess the Real-world Effectiveness of EVUSHELD™ (Tixagevimab/Cilgavimab) as Pre-exposure Prophylaxis Against COVID-19 Among Immunocompromised Patients in Israel' (*AstraZeneca,* 27 October 2024).

[44] See Exhibit EP/28 - **INQ000521827** Ordaya EE et al., 'Characterization of early-onset SARS-CoV-2 infection in immunocompromised patients who received tixagevimab/cilgavimab prophylaxis' (2022) Open Forum Infectious Diseases.

See Exhibit EP/29 - **INQ000521829**, Stuver R et al., 'Activity of AZD7442 (tixagevimab/cilgavimab) against Omicron SARS-CoV-2 in patients with hematologic malignancies' (2022) Cancer Cell.

See Exhibit EP/30 - **INQ000521820** Karaba AH et al., 'Omicron BA.1 and BA.2 Neutralizing Activity Following Pre-Exposure Prophylaxis with Tixagevimab Plus Cilgavimab in Vaccinated Solid Organ Transplant Recipients' (2022) medRxiv.

See Exhibit EP/31 - **INQ000521831** Conte WL, Golzarri-Arroyo L et al., 'Tixagevimab and Cilgavimab (*Evusheld*) boosts antibody levels to SARS-CoV-2 in patients with multiple sclerosis on b-cell deplete' (2022) Mult Scler Relat Disord.

that there remained uncertainty that *Evusheld* would prevent symptomatic COVID-19 caused by current Omicron variants in the vulnerable population who would potentially be eligible.

97. The "Dear Colleagues" letter was ultimately issued on 12 October 2022 in broadly similar terms to the prior drafts which AstraZeneca had seen.

98. AstraZeneca indicated to the UK Government that AstraZeneca would proceed to make *Evusheld* available to patients outside the NHS on a private basis. We did not feel that we could deny access to those who needed *Evusheld* any longer, although we were concerned that this would not result in equitable access and AstraZeneca would have preferred *Evusheld* to have been made available on the NHS. Accordingly, *Evusheld* became available on a private basis to patients in the UK in October 2022.

NICE appraisal process

99. AstraZeneca's involvement in the NICE appraisals for *Evusheld* took place entirely outside the reference period established in the Inquiry's Terms of Reference. However, I will briefly outline our experience of the process, as I understand it to be of interest to the Inquiry.

100. There were two NICE appraisals for *Evusheld.* One was a Multi Technology Appraisal (***MTA***) process and the other was a Single Technology Appraisal (***STA***) process. The MTA process appraised the clinical and cost-effectiveness of various interventions including *Evusheld* for treating people with mild COVID-19 at high-risk of progressing to severe COVID-19 and people with severe COVID-19. The Single Technology Appraisal (***STA***) process evaluated *Evusheld* for pre-exposure prophylaxis, rather than for treatment.

101. AstraZeneca engaged fully with both NICE processes. The MTA process began first, although the two appraisals overlapped. NICE scoping began in April 2022 for the MTA and in July for the STA, and AstraZeneca was formally invited to participate in each process in August 2022.

102. Ultimately, neither appraisal process recommended *Evusheld* for use by the NHS. The NICE Final Draft Guidance for the MTA and the STA was issued in February and May 2023, respectively, and the STA Technology Appraisal Guidance followed in June 2023 (TA900). The MTA was subject to appeal by

AstraZeneca and others, and new Final Draft Guidance was issued in April 2024, with the Technology Appraisal Guidance following in May 2024 (TA971).

103. One of the main challenges with the NICE appraisals of *Evusheld* (from AstraZeneca's perspective) was the review timeframe. We had wanted any evaluation of *Evusheld* to be rapid, so that guidance could be issued as soon as possible to support the provision of this product to high-risk patients (such as those who were required to continue to shield themselves from exposure to the virus). We considered that procurement via emergency means prior to full review was preferable to ensure quick availability to the most vulnerable groups following MHRA approval (essentially to be able to bridge the gap to allow protection for those at greatest risk over the winter months while NICE evaluated), in the same way as had happened for the COVID-19 vaccines and for certain other therapeutics (for example, Ronapreve).

104. The full appraisal process for pre-exposure prophylaxis took almost a year and the rapid evolution of the virus meant that by the time NICE came to issue its decisions, *Evusheld*'s efficacy against the newly circulating strains had been reduced. Towards the end of 2022, it transpired that new variants had started to emerge at speed, unlike the approximately six-monthly waves we had seen since the start of the pandemic. From this point, variant escape had taken place and *Evusheld* no longer demonstrated in-vitro neutralisation per live virus assays.

105. A related key challenge faced by AstraZeneca concerned the unprecedented dynamic nature of the evolving COVID-19 virus variants and the failure of the NICE committees to be able to flex their established appraisal processes to account for this in the data and methods used for evaluation. In particular, our view was that there should have been a more consistent and transparent framework to account for evolving data (such as in-vitro neutralisation data and RWE data) as part of the assessment to inform decision-making, and that there should have been more consultation on the applicable framework. This could have been used to demonstrate updated effective neutralisation rates.

SECTION H: FUTURE PANDEMIC PREPAREDNESS

106. As set out below, I believe there are a number of key lessons learned from AstraZeneca's experience of developing *Evusheld* that may assist the UK Government's future pandemic preparations.

The immunocompromised: unmet patient need

107. For the next pandemic, greater consideration should be given to the needs of immunocompromised patients. Vaccination is for the many, but we must not forget the few for whom it is not an adequate medical response.

108. There remains a strong need to support these individuals, and during the COVID-19 pandemic period of concern there was a clear unmet clinical need among this cohort, who were not adequately protected by vaccination. The evidence is clear that clinically vulnerable groups such as the immunocompromised continue to shoulder disproportionate health and financial burdens from COVID-19.[45] Additionally, there are social impacts on these groups affecting their overall quality of life, including ongoing limits to social contact and an inability to return to everyday lives. As life returns to normal for the majority, these people risk being left behind.

109. A deeper understanding and recognition of this diverse group is urgently required to help foster access to tailored and appropriate care, and treatment remains an unmet need.

mAbs

110. To ensure that we are prepared for the next pandemic, a broader prophylaxis response strategy is required, and AstraZeneca believes firmly in the ability of mAbs to support immunocompromised people in this regard.

111. mAb therapies which have the potential for prophylaxis should be treated on an equal footing to vaccines and should benefit from any expedition or acceleration which may be available to vaccination options (including with respect to regulatory approval and / or procurement pathways).

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[45] See Exhibit EP/32 - **INQ000521807** AstraZeneca, 'COVID-19 continues to disrupt the health and lives of the immunocompromised' (*AstraZeneca*, 17 July 2023).

Discovery and pre-clinical development

112. Sufficient funding at the discovery and early development phase is essential to facilitate success, and to bring promising candidates through early pre-clinical testing as quickly as possible. Our partnership with the United States Government was very effective in this regard and was a key enabler in the development journey for *Evusheld*. This work built on the groundwork that had been laid with the DARPA P3 pandemic preparedness programme and allowed the team to move quickly once the pandemic was declared.

113. Early and sufficient access to samples from convalescing patients is essential to the discovery and screening phase. Collaboration was key to this element, as well as more generally to our success in the early development phase. The success of *Evusheld* was achieved through effective collaboration between key stakeholders, including government, academic institutions and industry.

114. We should be considering now the sorts of public-private collaborations and partnerships that it would be useful to put in place to enable swift and effective mobilisation in the future.

Clinical development

115. Again, AstraZeneca received support through the clinical development phases for *Evusheld* from the United States Government, and this support was instrumental.

116. We would welcome further progress and engagement on the need to facilitate innovative clinical development and approval pathways, such as increased facilitation of immunobridging trials. Immunobridging is an approach to clinical trials used to infer effectiveness of a potential new medicine through an accepted surrogate for efficacy. These trials are designed to demonstrate equivalent activity for a control with prior clinical efficacy data and a candidate therapeutic. In the case of mAbs for the treatment or prevention of COVID-19, the principle is to show that a new mAb neutralises current SARS-CoV-2 variants at least as well as previous mAbs neutralised earlier variants, allowing "*bridging*" from the mAb with known clinical efficacy to the new mAb with unknown clinical efficacy. Immunobridging trials can help reduce development time and accelerate access to important new medicines. Immunobridging has been recognised since the late 1990s and has supported approvals for COVID-

19 medicines and other disease areas including flu, HPV and pneumococcal pneumonia. We encourage the MHRA to continue to look at this and other strategies for facilitating efficient clinical trials.

Regulatory process

117. In AstraZeneca's view, the MHRA was exemplary with respect to the regulatory approval process for *Evusheld.* It engaged with AstraZeneca early and made its expectations clear, for example with respect to the kind of application which it considered to be appropriate, and the data which it required. The MHRA agreed to undertake expedited rolling review, and its turnaround times were very quick.

118. The MHRA also introduced welcome flexibility into certain aspects of the process, for example, with respect to the format of submissions (e.g. allowing online submissions), which made the process more efficient for AstraZeneca.

Manufacturing

119. I have outlined above the challenges of securing scaled-up manufacturing capacity for *Evusheld*. There was no spare UK capacity available during the pandemic, and little capacity globally.

120. This is an obvious example of where public-private collaborations and partnerships could be effective in ensuring that capacity can be scaled up as needed to meet demand. The specialised nature of biologic medicine manufacturing means that this cannot be achieved as a quick and urgent fix during a pandemic situation, and investment is needed now to ensure that the foundations are put in place so that they can be scaled up at pace.

UK Government procurement process

121. AstraZeneca considers that there should be an expedited process for appraising therapeutic medicines for procurement at times of an established or emerging national emergency. Such a process should retain the best of NICE's appraisal processes to address uncertainty and to form a data driven view based on the available clinical and health economic data, while at the same time allowing the NHS to act with urgency to assess new treatments without having to create a new ad hoc process. This would allow future governments

and NHS leaders to rely on a process which, whilst still robust, recognises the need to act with urgency during a time of crisis.

122. On reflection, the UK Government did not establish an appropriate mechanism for assessing the evidence behind *Evusheld* and reaching a timely procurement decision on the basis of clinical and scientific assessments. AstraZeneca considers that a pre-exposure preventative drug such as *Evusheld* would have more appropriately fitted within the remit of the Joint Committee on Vaccination and Immunisation (and the VTF) during the COVID-19 pandemic.

123. AstraZeneca's experience of working with the VTF was that the VTF was led by experts with knowledge of all aspects of the development, procurement and distribution of a vaccine. This group was able to make decisions swiftly and on the basis of expertise and scientific consensus. This was made possible because it was generally understood and appeared to be the view of the UK Government that vaccines needed to be developed and procured to enable the general population to emerge from pandemic controls.

124. However, by the time that the TTF/ATTF began to consider *Evusheld*, it appeared as though there was no consensus within those groups as to whether this type of medicine should be procured in principle. In the absence of an established process for assessing such a product on an expedited basis, the UK Government appeared unsure whether to continue to operate outside of the traditional NICE appraisal route (e.g. via the expedited and purposeful approach adopted for vaccine procurement) or instead to subject *Evusheld* to a standard NICE process.

125. There also seemed to be a reluctance on the part of the UK Government advisors to accept RWE gathered from *Evusheld*'s successful deployment in other countries to support the UK procurement decision. We would urge the UK Government to build in a process to take into account statistically significant, robust RWE data worldwide.

126. With my concluding remarks, I would like to underline that AstraZeneca is very proud of what we achieved with *Evusheld*. In a very short space of time, we brought to market an effective product which was approved by regulators in more than 30 countries around the world. It fulfilled a specific unmet need among a vulnerable population in those countries which procured it, saving

lives and enabling a measure of independence to those individuals that otherwise may have been denied. I am grateful for the tireless effort of my colleagues at AstraZeneca and for the collaboration of our partners worldwide, without whom, this extraordinary achievement would not have been possible. *Evusheld* did not, ultimately, play a part in the UK's NHS pandemic response. However, we hope that the UK will, in the future, be among the countries using mAbs to protect the clinically vulnerable in society, which should be considered a priority group.

Statement of Truth

I believe that the facts stated in this witness statement are true. I understand that proceedings may be brought against anyone who makes, or causes to be made, a false statement in a document verified by a statement of truth without an honest belief of its truth.

Signed Personal Data

Dated: 11-Dec-2024