NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

Decision of the panel

Introduction

1. An appeal panel was convened on 2 and 3 May 2023 to consider an appeal against the final draft guidance document (FDG), to the NHS, on Molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

2. The appeal panel consisted of:

• Professor Jonathan Cohen	Chair
• Dr Justin Whatling	Non-executive director, NICE
• Chris Rao	Health service representative
• Paul Trueman	Industry representative
• Catherine White	Lay representative

3. None of the members of the appeal panel had any new or undeclared competing interests to declare.

4. The panel considered appeals submitted by Merck Sharp & Dohme (MSD), Gilead Sciences (Gilead), and AstraZeneca (AZ).

5. MSD were represented by:

• Stephen Hocking	Legal representative, 11KBW
• Grant Castle	Legal representative, Covington

	and Burling LLP
• Claire Grant	Head of Health Technology Assessment and Outcomes Research
• Dionysios Ntais	Associate Director, Head of Health Technology Assessment and Outcomes Research
• Janet Lord	Medical Advisor

6. Gilead were represented by:

• Gordon Lundie	Director of Market Access
• Leena Sathia	Medical Director for COVID-19
• Mirko Von Hein	Associate Director, Market Access
• Kathryn Coville	Senior Legal Director
• James Jarrett	Senior Director

7. AZ were represented by:

• Oonagh McGill	Market Access Director
• Daniel Squirrell	Head of Market Access
• Jurgens Peters	Head of Vaccines and Immune Therapies
• Dom Hornblow	Legal Director
• Phil Allison	Franchise Head

8. In addition, the following individuals involved in the evaluation were present and available to answer questions from the appeal panel:

• Professor Stephen O'Brien	Chair, Technology appraisal committee C
• Dr Richard Nicholas	Vice-chair, Technology appraisal committee C
• Professor Rachel Elliott	Member, Technology appraisal committee D

• Helen Knight	Director of Medicines Evaluation, NICE
• Ross Dent	Associate Director, NICE
• Adam Brooke	Technical Adviser, NICE
• Professor Matt Stevenson	Evidence Advisory Group representative

9. Professor Matt Stevenson declared that he had received payment from AZ rare diseases for work in a different area. None of the other members of the appraisal committee or appeal panel had any new or undeclared competing interests.

10. The panel's legal adviser Alistair Robertson, DAC Beachcroft, was also present.

11. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

12. There are two grounds under which an appeal can be lodged:

    Ground one: In making the assessment that preceded the recommendation, NICE has:

    (a) Failed to act fairly; and/or

    (b) Exceeded its powers.

    Ground two: The recommendation is unreasonable in light of the evidence submitted to NICE.

13. Dr Mark Chakravarty, NICE Lead Non-executive Director for Appeals, in preliminary correspondence had confirmed that MSD (molnupiravir) had valid grounds for appeal under Grounds 1(a), 1(b) and 2; Gilead (remdesivir) had valid grounds for appeal under Grounds 1(a), 1(b) and 2; and AZ (tixagevimab and cilgavimab) had valid grounds for appeal under Ground 1(a).

14. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The majority of infected people will remain asymptomatic or have mild to moderate symptoms including fever, cough, headache, fatigue, breathing difficulties, loss of smell, loss of taste, or mild pneumonia. Some patients will develop more severe symptoms of dyspnoea, hypoxia, respiratory failure, systemic inflammatory response, shock, and multiorgan dysfunction. Immunocompromised people and those with pre-existing respiratory and cardiovascular conditions have a worse prognosis. Standard management involves the treatment of symptoms through supportive care and corticosteroids.

15. The evaluation that is the subject of this appeal provided advice to the NHS on the use of the neutralising antibodies tixagevimab and cilgavimab; antiviral medications molnupiravir and remdesivir, within their marketing authorisations for treating people with symptomatic COVID-19.

16. The numbering of appeal points in this document reflects those that were used during the hearing. The text of this document does not represent a verbatim account of the proceedings nor a documentation of the order of events that took place but rather, provides a brief summary of the appellant and committee submissions for the points that were discussed relevant to the decisions of the panel.

17. Before the appeal panel inquired into the detailed appeal points the following made preliminary statements: Stephen Hocking on behalf of MSD, Gordon Lundie on behalf of Gilead, Daniel Squirrell on behalf of AZ, and Professor Stephen O'Brien on behalf of NICE.

Appeal Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly.

MSD appeal point 1(a)1: NICE acted unfairly by following an ad-hoc process that departed from the Manual.

18. Stephen Hocking, for MSD, stated that NICE failed to act fairly by following an ad hoc process that departed so far from the published process that NICE could not be said to have performed a Multiple Technology Appraisal (MTA) at all. He stated that following a process materially outside NICE's published processes is unfair, regardless of the actual merit of the process followed, and that this argument succeeds even if the actual processes followed had, in and of themselves, been fair. He argued that the process followed in this case was indeed materially outside NICE's published processes as set out in *NICE health technology evaluations: the Manual* (the Manual), and that this is an argument of principle rather than fairness understood in a narrow sense.

19. Stephen Hocking referenced Regulation 2 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 ("the NICE Constitution and Functions Regulations") which defines a technology appraisal recommendation as "a recommendation made by NICE following an appraisal of the benefits and costs of a health technology conducted by NICE in accordance with NICE's published methods and processes for appraisal of health technologies that results in a positive assessment". He argued that a recommendation made after any other process is, by definition, not a technology appraisal (TA) recommendation.

20. Stephen Hocking referenced Regulation 7(9) of the NICE Constitution and Functions Regulations which states that "NICE must establish a procedure for the appraisal of health technologies and must consult such persons as it considers appropriate in establishing the procedure". He stated that it was obviously unfair for NICE to be free

to depart without consultation from processes that it can only adopt after consultation. Finally, he stated that neither NICE nor the Secretary of State for Health and Social Care can legally depart from these regulations.

21. Stephen Hocking outlined the following examples where in MSD's view the committee deviated from the Manual detailing the processes and methods that should be followed for technology appraisal.

    a. He stated that, contrary to paragraph 5.5.8 and 5.6.2 of the Manual, there was no initial evidence submission from companies and that they were only allowed to submit targeted evidence to review after the external assessment group (EAG) had done the bulk of its work. He stated that the process and methods require an evidence submission, before any EAG review.

    b. He stated that paragraph 5.5.1 of the Manual requires distinct phases; submission, review, and evaluation; and that these phases were condensed into two stages not three and run in parallel.

    c. He stated that paragraph 3.3.4 of the Manual requires systematic review of relevant evidence using a pre-defined protocol. This was not undertaken resulting in a biased selection of studies.

    d. He stated that limits were placed on the type of evidence that the companies were permitted to submit and that the EAG considered. According to paragraph 6.2.5 of the Manual, companies should submit all evidence available, and the committee should consider all evidence presented. In this evaluation the EAG limited itself to published evidence and companies were limited in what unpublished data they could submit. MSD sought to submit real-word evidence (RWE). He

stated that whilst MSD acknowledges the limitations of RWE, the Manual does not say RWE will be excluded a priori.

22. Stephen Hocking concluded that these points taken individually and cumulatively demonstrate that whatever process was followed, this was not an MTA process, and therefore the output is not MTA guidance.

23. Grant Castle, for MSD, stated that MSD sought clarification about whether the Secretary of State might have given directions for NICE to deviate from published processes. He stated that both iterations of the directions from the Secretary of State to NICE (3/3/21 and 19/7/21) required an MTA. There was no requirement for amendment or resequencing. He stated that MSD did not understand where the need for urgency came from, and why NICE felt it needed to re-sequence or omit key elements of the MTA process.

24. Claire Grant, for MSD, stated that there was an unpredictability throughout the evaluation because the process was changing. For example, was RWE in or out, what were companies required to submit, and was the living systematic literature review (SLR) and network meta-analysis (NMA) keeping up with what is published? She stated that this left MSD feeling wrong-footed, and that they could not support the process because they did not know what the process was. She stated that MSD had submitted 18 publications on RWE relating to molnupiravir which were not considered. She stated that failure to consider and discuss this evidence was not only different to a usual evaluation process, but this was unfair as the randomised evidence considered was already out of date, having been acquired from a pandemic, largely unvaccinated, population. She cited treatment of the OpenSAFELY data as being particularly unfair.

25. Professor Stephen O'Brien, for NICE, stated that some elements of this MTA were different, however COVID-19 was exceptional, and some flexibility seemed reasonable. He stated that because of the

unusual nature of COVID-19 numerous drugs were expeditiously approved, inevitably resulting in the introduction of drugs that were not effective. He explained that the job of the committee was to apply a more robust and stringent approach than had been taken earlier. He said that the committee applied rigorous approaches, and tried to align the evaluation with the standards that would normally be used in a calm collected way. He stated that companies had the usual opportunities to tell NICE what they got wrong. He stated that draft conclusions went out to consultation and that the appraisal committee in the second meeting considered thoughtfully, and took on board, various aspects of consultation feedback.

26. Ross Dent, for NICE, in seeking to explain why NICE took a different approach for this TA stated that timing was an important consideration. He stated that whilst it was not appropriate at the height of the COVID-19 pandemic to evaluate therapies, new medicines are not usually adopted by the NHS without evaluation. He stated that NICE knew that the NHS would need guidance in time, and that they would need to move quickly. NICE were also conscious of how long an MTA takes and the unique factors associated with COVID-19. He explained that NICE thought that building a model before formally starting evaluation would put them in the best position to formulate a recommendation. He stated that when NICE started the process of building a model in March 2022 it was unclear when the NHS might need guidance, but a provisional timeline was anticipated with a committee meeting in October 2022, to potentially provide guidance in time for winter 2022. Once NICE had completed the modelling phase it had become clearer that NICE guidance would be needed by the end of March 2023 when the antivirals and therapeutics taskforce, which had been the mechanism for providing these treatments to the NHS, would be disbanded. He stated that at that point, commissioning would pass to the NHS. It was consequently decided to proceed with the committee meeting in October. He stated that the alternative would have been to take much

longer and potentially leave a gap between the taskforce closing and issuing guidance to the NHS.

27. Ross Dent then explained why the committee took the approach that it did, how in the committee's view the process eventually followed was close to the established MTA process, checks and balances introduced to ensure fairness, and how the committee communicated what they planned to do to stakeholders. He stated that NICE normally start by assessing the landscape and the evidence, but that in this disease area there was no guarantee that things would not have substantially changed as NICE moved forwards with the evaluation. He stated that they felt that getting the basics of a model right, consulting, getting agreement where possible, then having a shorter time between starting evaluation and getting committee decisions was the best way to get a decision before it was out of date, and enabling companies to submit evidence they felt was relevant. He stated that NICE communicated that this was the planned approach to stakeholders at an information meeting in April 2022. He stated that the process developed in part from comments from stakeholders when NICE produced the draft scope. He said that NICE set out the comments received and went through the process statement NICE intended to follow and the protocol that the EAG would follow. He stated that NICE invited all the companies, patient, and professional organisations to come to that meeting, discuss with them, and set expectations for how the evaluation would proceed. Instead of the EAG starting the literature reviews from scratch, he explained that they decided to rely on publicly available meta-analyses. The EAG estimated that a SLR would take 9 months. He stated that NICE did not feel that was a reasonable use of resources as with a changing evidence base, this would be out of date by the time they came to use it. He stated that NICE were aware of global efforts to produce an NMA, and that they were being constantly updated so should not miss key evidence. He stated that such NMAs were the basis of recommendations in clinical guidelines and widely accepted by

stakeholders. Ross Dent stated that he could go into technical points as to what exactly the Manual requires and why he thinks that those requirements were met by the work done by the international groups who performed the NMA.

28. Ross Dent acknowledged that NICE followed a different process to that set out in the Manual, for what the committee considered to be appropriate reasons. When discussing what checks and balances were introduced to ensure fairness, he stated that all stakeholders were able to comment and that NICE asked companies to provide evidence not included in the EAG report. He stated that NICE thought it was sufficient to do that without duplicating evidence already submitted and considered. Finally, he explained that following the first committee meeting there was consultation on draft guidance.

29. Helen Knight, for NICE, stated that the approach was discussed with stakeholders throughout, that NICE explained the approach they were going to take, why NICE were going to take it, and the rationale was clear to the companies. She stated that NICE feel that they have undertaken a rigorous and reasonable evaluation but with a slightly re-sequenced approach. She said that the Department of Health and Social Care were supportive of the approach taken to deliver the outputs.

30. Helen Knight in response to a direct question from the appeal panel chair about why this approach was not more widely adopted if it was quicker and equally robust, stated that this is exactly what NICE should be thinking about doing. She stated that the aim of NICE is to get access to best care quickly and to deliver value to the taxpayer. She said that NICE need to think about doing things in a slightly different way and that COVID-19 was a great opportunity to explore that. She stated that a lot of information had already been collated and analysed, and NICE took the approach that as there was good existing information available, this meant that things could be done in

a different way. She stated that NICE are currently consulting on a different rapid update process and are looking for ways to do things quicker.

31. In response to a direct question from the appeal panel chair about whether all aspects of the usual MTA process were performed, Ross Dent stated that a key difference was that the time from stakeholder submission to decision was reduced. He said that the change was necessary, as unlike COVID-19, most diseases do not change over the course of assessment.

32. Ross Dent in response to a direct question about whether the quality of the MTA was compromised because it was performed more quickly, stated that he did not think so. He said that many of the steps highlighted by the appellants as being absent in the process used in this review would not ordinarily occur in an MTA. For example, initial discussion and evidence submission would not ordinarily happen in an MTA and the evidence submission was broad enough.

33. Ross Dent stated that they did not invite submission of a model because they had already spent significant time and resources developing and consulting on the EAG model. He said that stakeholders had commented and the EAG had revised it. He explained that it did not seem appropriate to invite submission of seven models from companies and then go through the process of critiquing them when NICE already had a model that all stakeholders had agreed upon.

34. Ross Dent stated that the committee felt it was appropriate to use an SLR performed by an external group as the Manual only mandates assessment based on synthesis of publicly available evidence. The external groups followed a clearly defined protocol; that was published, and publicly available for comment. He stated that NICE did not think that the Manual strictly requires the EAG to perform the systematic review themselves as long as it was robust.

35. Ross Dent was asked about the status of the process statement, which is not a routine part of the evaluation process. Ross Dent stated that they have set out position statements in the past to guide committees. He explained that the process statement here was an attempt to be as transparent as possible to all stakeholders. He said that NICE explained this and the status of the document at the stakeholder information meeting in April 2022.

36. In response to a direct question about whether any feedback or comments were received from stakeholders on the process statement, Ross Dent stated that the stakeholder information meeting held in April 2022 was a discussion about the process statement outlining how the evaluation would be undertaken and this meeting was not a formal consultation.

37. Stephen Hocking stated that he did not think that NICE asserted that there was consultation on the process statement. He argued that what happened in publishing the process statement was not a consultation at all as NICE's mind had already been made up.

38. Claire Grant stated that MSD did not really know what was going on. She stated that they were asked questions and told there would be changes but did not understand the impact it would have on the process and how far it would depart from the usual technology appraisal process. She said that a number of conversations took place within MSD about whether they should step away from the process because the company were so blind to what was going on. She stated that MSD was always appreciative of flexibility that is patient focussed and felt an obligation to be a good corporate partner. She said that she could not identify any tangible examples of where the concerns of MSD had resulted in any meaningful changes.

39. Helen Knight in response to the above statement by Claire Grant and a question from the appeal panel chair about whether there could have been more transparency, admitted that the process statement

and underlying rationale could have been clearer and more transparent. She stated that she did not believe that the changes made were so significant that they would compromise anyone's ability to participate or get the right information in front of the committee to inform the clinical and cost effectiveness of those treatments.

40. Helen Knight stated that it was important to refer to NICE's principles. She explained that principle 2, point 10, stated that "We are required to follow our documented processes and methods and are accountable for the decisions that we make. Sometimes it is appropriate to depart from the documented processes and methods for particular recommendations. When this happens, we clearly explain our rationale in the guidance or standard, or in accompanying documents". She stated that the process statement issued in April 2022 was intended to signal that this was a different situation where NICE was deviating slightly from published process according to guidance from NICE's principles. She stated that the NICE team have said why they think the approach that they have adopted was robust, possibly even more robust than the usual process.

41. Stephen Hocking stated in response to Helen Knight's comment's about NICE's principles that if they say that NICE can depart from processes, then legally they are wrong. He also said that the principles do not help very much as they are internally contradictory. He noted that the principles record that NICE is required to follow published process.

42. Stephen Hocking concluded that Ross Dent had acknowledged that a different process was followed other than the one set out in the Manual. He stated that NICE are not permitted to depart from their usual appraisal methods and processes, no matter how rigorous and fair. He referenced the tenth slide from the first meeting and made the point that the order in which the steps of an evaluation are performed matters. He said that it does not matter if the revised timeline is

equally valid or even better; it has to be consulted upon and formally adopted. He stated that whilst the process statement was published as an exercise in transparency, this was not a consultation, as Ross Dent has fairly acknowledged. He stated that it was presented to stakeholders as a finalised process with explanation but no opportunity to respond to a consultation to change the process. Finally, Stephen Hocking acknowledged there was no doubt that the evaluation was done by intelligent people acting with the best of intentions and responding to an acknowledged need. He stated that however, from the start it went wrong when NICE departed from the process and the MTA steps were re-sequenced. He said that MSD did not understand the perceived need for urgency, as at least some of the drugs, including molnupiravir, were already procured and stockpiled for NHS use.

43. Professor Stephen O'Brien concluded that as he looks at the latest submissions and analyses, he has not seen anything to make him think that the appraisal committee had made a "howler" with regard to these drugs. He stated that as a clinician who has watched patients die, he really did feel a sense of urgency to ensure we get the most clinically effective drugs with established evidence, and that he was conscious that the NHS was potentially spending hundreds of millions of pounds on drugs that might not be effective.

44. The appeal panel concluded as follows:

45. It was common ground between the NICE appraisal team and the appellants that there were multiple occasions in which this evaluation deviated from NICE's published procedures on MTA including in particular that:

    a. Firstly, there was re-sequencing of the appraisal process. This meant that the SLR was not informed by company evidence submission and that the economic model was constructed

before company evidence submission which might have identified additional relevant real-world data.

b. Secondly, the time allowed for many of the stages of the appraisal process was shortened. This resulted in companies being invited to make focused evidence submissions rather than the usual comprehensive evidence submissions, not being permitted to submit an economic model, and having limited opportunity to engage and comment.

c. Finally, the form of some stages of the process such as the SLR, took an entirely different form from that described in the Manual.

46. The appellants in written submission prior to the appeal panel hearing and in oral submission during the hearing argued that resequencing compromised the rigour of the appraisal process. They argued, for example, that modelling was performed prior to company submissions and SLR, consequently it was not informed by the most relevant evidence.

47. The appellants argued that stakeholder engagement was compromised by the shortened time allowed for stages of the processes such as evidence submission, and unfamiliarity with the appraisal process resulting from re-sequencing. They argued that this resulted in unfairness.

48. The appeal panel felt that it was plausible that the abbreviated timeframe and re-sequenced evaluation may have had an impact on both the quality of the appraisal process and the ability of stakeholders to engage with this process.

49. The appellants also argued that any deviation from the processes defined in the NICE manual on health technology evaluation represented procedural unfairness.

50. The appeal panel agreed that in the case of this evaluation, deviation from the processes defined in the Manual, without consultation and/or stakeholder agreement, was unfair. The appeal panel would have considered this to be the case, even if the evaluation was considered to have been performed with the same or better quality and rigour than if it had been conducted according to the usual processes defined in the Manual.

51. The appeal panel did not consider that the process document for this evaluation represented sufficient mitigation for the unfairness resulting from deviation from the normal MTA processes described in the Manual.

52. The appeal panel concluded, therefore, that there was evidence of procedural unfairness on this issue and upheld the appeal point.

MSD appeal point 1(a)2: NICE acted unfairly because of ad hoc process changes during the appraisal that individually or taken together led to unfairness.

53. MSD appeal point 1(a)2 was heard together with MSD appeal point 1(b)2 and consequently the oral evidence submitted to the hearing by the appellant and representatives of NICE are summarised for both appeal points in the following paragraphs.

54. Stephen Hocking, for MSD, stated that even if all the steps of an MTA were present but in a different order that would still result in unfairness. He stated that the panel should consider the cumulative unfairness of the departures from the usual process. He stated that it was clear that the EAG was left with considerable discretion to exercise its judgement about how the evaluation should be conducted. He explained that the process statement stated that the EAG would pragmatically assess where time savings could be made without impacting on main conclusions. He argued that the EAG should not have made decisions about whether an SLR or probabilistic sensitivity analysis should be undertaken, and what

evidence should be admitted and excluded as this amounts to the EAG becoming a co-decision maker with the committee.

55. Claire Grant, for MSD, stated that because of the re-sequencing an assumption was made that the PANORAMIC definition of high risk was the correct definition for a high-risk population. She stated that by the end of the first committee meeting, this had been abandoned and the McInnes definition was adopted. She argued that if the usual process had been followed then this would have been evident before the first committee meeting. With reference to the UK randomised controlled trial (RCT) PANORAMIC, she said that the mechanism by which it was introduced into the process left the company feeling that the goalposts had moved. She stated that data was shared in the week before the committee meeting, with no opportunity for companies to give views in advance of the meeting. She stated that the EAG partially stepped into a decision-making role, and this blurred responsibility for decision making. She cited the example of the EAG making the decision that there was insufficient data to consider subgroups in detail and this led to a decision after the first committee meeting with the result that high-risk patients had no treatment options. She cited a further example in which the EAG did not consider the logistics of drug administration, and the change from a pandemic to endemic setting. She said that throughout the evaluation the company were trying to support the process, but because the EAG and committee were not adopting their usual roles, this was very challenging.

56. Professor Stephen O'Brien, for NICE, stated that the EAG was not making decisions. He said that the committee made decisions based on evidence from the EAG. In particular, with reference to the PANORAMIC and McInnes definition of high-risk patients, he explained that the decision about what definition to use was taken by the committee. He acknowledged that the EAG made assumptions

on how to model things but was very clear that the EAG provided the evidence, and the committee made the decisions.

57. Ross Dent, for NICE, stated that the EAG did make decisions about what to present in the report that went to the first appraisal committee meeting, however the committee could have asked the EAG to perform a probabilistic sensitivity analysis. He stated that he did not believe that decision-making power had been taken away from the committee in any of the examples that were cited.

58. The appeal panel chair referred to the appraisal protocol which stated that “This research is not aligned with a typical NICE multiple technology appraisal (MTA) primarily due to the shortened timescales which will require the EAG to pragmatically assess where time savings can be made without impacting on the main conclusions. NICE will be kept informed of such decisions.” In response to a direct question about whether the EAG were making judgements and informing NICE, Ross Dent stated that he recognised that this was written in the protocol but did not think the EAG made any decisions other than about the SLR.

59. Stephen Hocking stated in response that MSD were not concerned that the EAG was writing bits of the guidance, but that the EAG made decisions such as not to put the RWE before the committee. He stated that as far as the company were aware, the committee never had the chance to decide whether its conclusions on PANORAMIC would be altered if it considered RWE. He stated that the company felt that "gatekeeping" of that nature by the EAG is not allowed, particularly in absence of any SLR or agreed process.

60. In response to a direct question from appeal panel members about when the EAG actually made decisions without committee oversight, Claire Grant cited the decision to use the SLR, the inclusion of PANORAMIC data into the NMA and the presentation of

PANORAMIC data to the committee, the decision not to perform a probabilistic sensitivity analysis and the definition of high-risk patients.

61. Professor Stephen O'Brien stated that committee had all the submitted RWE. He stated that the committee considered it but might not have debated it a lot during the meeting. He said that PANORAMIC recruited over 26,000 patients and it was right to place weight on it and to consider it carefully. It featured in the NMA. He stated that the appraisal committee focused on the evidence that had the greatest impact on their decision making.

62. Ross Dent stated that the living NMAs are based on SLRs. He stated that you would not expect an SLR to identify RWE. The checks and balances were that the manufacturers were able to submit any evidence they wished.

63. Claire Grant stated in response to this point that whether or not an SLR identified RWE would depend on the inclusion criteria of the SLR.

64. Grant Castle, for MSD, stated that when the evaluation was commenced the process statement and protocol made clear that only published RCTs would be considered, particularly those in the living NMA, and this is the basis on which MSD participated. He stated that unpublished data such as the PANORAMIC trial, and "cherrypicked" RWE such as the OpenSAFELY trial were then included and became highly influential. He explained that MSD were trying to respond to an evolving concept of the acceptable evidence base and tried to submit its own RWE that it felt helped contextualise OpenSAFELY and PANORAMIC. He argued that whilst the appraisal committee say that they were aware of the MSD submission of RWE there is no evidence that it was considered, and if it was considered, this was done in an opaque and non-transparent manner.

65. In response to the contention by Ross Dent that the invitation to companies to submit evidence mitigated the absence of a dedicated SLR, Grant Castle stated that a company has to understand the ground rules for evidence submission. He stated that those goalposts were constantly moving, and that the company was trying to catch up with a process that it did not understand and was constantly changing.

66. In response Ross Dent stated that he did not believe that the process statement stipulated that only RCT evidence would be considered, nor was this dictated when NICE invited targeted submissions from companies.

67. Professor Matt Stevenson, for NICE, stated that from the perspective of the EAG he did not think that they made any decisions that they would not ordinarily make in a normal MTA, and certainly not without confirming these with NICE. He stated that there was no evidence of where they had done that apart from potentially in the case of the probabilistic sensitivity analysis (PSA). He said that had the committee asked the EAG to do anything differently they would have done that.

68. The appeal panel concluded as follows:

69. The appeal panel agreed with the appellants that the individual and cumulative effect of the abbreviated timeframe and re-sequencing of the evaluation had an impact on both the quality of the appraisal process and the ability of stakeholders to engage with this process.

70. The appeal panel agreed with the appellants that deviation from the processes defined in the Manual, without stakeholder agreement, was generally unfair irrespective of the impact that this may have on the quality of the MTA. The panel considered that the factors relevant to this appeal point overlapped considerably with those relevant to MSD

appeal point 1(a)1, and that its reasons for upholding appeal point 1(a)1 applied equally to appeal point 1(a)2.

71. The appeal panel concluded, therefore, that there was evidence of procedural unfairness on this issue and upheld this appeal point.

MSD appeal point 1(a)3: NICE acted unfairly because the Appraisal Committee unfairly: (1) Failed to take adequate steps to identify relevant evidence. (2) Failed to consider relevant RWE about molnupiravir, particularly given its recognition of the "significant limitations" of the clinical evidence used in the appraisal and resulting uncertainty and the alleged particular relevance of the RWE that MSD presented. (3) Treated RWE inconsistently.

72. Claire Grant, for MSD, stated that it was apparent that there was confusion. She stated that the living NMA, and whether it would include elements of RWE was not really understood. She stated that it started reasonably, but that the inclusion of PANORAMIC data changed things. She argued that this trial was not performed in the right population. She said that MSD felt "horribly wrongfooted" and were "running to catch up." She stated that MSD submitted 18 references (not all of which were necessarily strongly supportive of molnupiravir), but that the only RWE talked about in the second appraisal meeting was OpenSAFELY which did not answer the question of what patients should do who could not reach an intravenous infusion chair.

73. In response Professor Stephen O'Brien, for NICE, stated that that it would be unrealistic for the EAG to critique all submitted RWE and incorporate it into the modelling. He acknowledged that the PANORAMIC study population was broader than McInnes. He stated that the appraisal committee considered this and judged that this did not invalidate the study. He explained that there was not a perfect study, but the committee considered everything that was submitted. He stated that the committee did not go through every single study in the meeting but focused on the evidence that they thought had most

importance[1]. He explained that the committee settled on a low efficacy scenario taking all the evidence as a whole. At that level not only was molnupiravir unconvincingly clinically effective it was also not cost-effective. In summary he stated that the committee considered all the evidence carefully and came to thoughtful conclusions.

74. In response, the appeal panel chair accepted that it was not the role of the committee to do the detailed work on every point of evidence, but asked whether it would not be expected that the EAG should appraise all the available evidence and present the committee with a view, and whether it had done so.

75. Adam Brooke, for NICE, stated that the committee followed the Manual and the framework when considering MSD submissions. He stated that NICE had a strong preference for PANORAMIC, a high-quality RCT, however acknowledged the need to search beyond RCTs to resolve residual uncertainties. He explained the team then considered what were the residual uncertainties. He stated that the generalisability of PANORAMIC data to the McInnes population was a concern, however, the committee considered the MSD evidence and judged it to be irrelevant to the decision problem.

76. Professor Rachel Elliott, for NICE, stated that the RCT data available to the committee including MOVe-OUT and PANORAMIC demonstrated the unconfounded treatment effect. She stated that all

[1] To assist readers, we explain here that the appraisal team modelled low, mean and high efficacy scenarios for each intervention compared to the standard of care, based on the 95% confidence intervals and median estimates of efficacy generated by the SLR. It was considered appropriate to use the mean efficacy scenario in the base case analysis if all the determinants of an intervention's efficacy were unchanged from when the clinical trials informing the SLR were performed, for example, the prevalent variant or the standard of supportive care in the clinical trials. Where important determinants of a treatment efficacy could be said to have changed following completion of the trial, limiting the generalisability of the trial to current clinical practice, a high or low efficacy scenario could be adopted. As in most cases uncertainty about generalisability related to concern that a therapy may be less efficacious in clinical practice compared to data from the trials informing the SLR the low efficacy scenario was frequently used in preference to the mean efficacy scenario and the high efficacy scenario was not used.

RCTs have limitations in terms of generalisability. She stated that PANORAMIC is an RCT in the target population. She explained that one of the problems faced by the appraisal committee was that the McInnes risk factors were not exactly covered in PANORAMIC, including people over 50, and therefore the committee were concerned that hospitalisation in PANORAMIC might be an underestimate. She stated that consequently there was some residual uncertainty and therefore the committee considered RWE. In addition to RWE identified by NICE a lot of RWE was supplied by MSD. She explained that the aim of the committee in considering RWE was to resolve concerns about hospitalisation rates in high risk and vaccinated populations. She stated that the studies used quite a mix of risk factors, for example, there were more immunocompromised patients in PANORAMIC than MOVe-OUT. She said that the OpenSAFELY cohort was a generalisable population directly relevant to the population of interest, and therefore the committee had to take that data seriously. She stated that this huge population level dataset enabled them to look at the impact in the highest risk McInnes population. Finally, she explained that she recognised that the value of RWE is more limited which is why it is lower down in the hierarchy of evidence than RCT and consequently the committee would not want to use RWE in lieu of RCT data unless essential.

77. In response to a question from the panel, Adam Brooke stated that no formal quality assessment of the RWE was undertaken. He stated that the research question was the generalisability of the RCT to the McInnes population. He said that quality assessment of RWE is difficult but can be performed heuristically. He argued that none of the RWE submitted by MSD was particularly relevant. In particular, none of the studies were from the UK and sample sizes were small. Taken in the context of what evidence the committee had, OpenSAFELY exactly represented the population under consideration. He argued that the small, mostly irrelevant, studies from MSD were not as relevant as data from OpenSAFELY. He said that he was not sure

how this could have been done in a formalised framework and noted that there was no formal assessment of the quality of RWE in MSD's submission.

78. Ross Dent, for NICE, stated that there is a tension between comprehensiveness and brevity. He said that they could not discuss all of the submitted evidence in the committee meeting, which was already long. Similarly NICE could not discuss all the evidence submitted in the FDG.

79. MSD were asked by the appeal panel chair to respond to the assertion from the NICE team that the submitted RWE was not sufficiently contributory to inform the decision making. In response Stephen Hocking, for MSD, stated that he agreed that the appeal hearing have heard that, but are none the wiser on what basis that is said. He argued that this is a simple appeal point; MSD submitted 18 studies that it says were relevant, somebody needed to look at them, apply some objective inclusion or exclusion criteria, and feed the result of that analysis to the committee. He said that he was not aware of anything in the documentation that says this has happened and cannot point to anything that would have been in front of the committee or that evidences any discussion of MSD's evidence. He said that he is not setting the bar very high here; all this needed to be done as a process point.

80. Adam Brooke stated that this evidence was in the committee papers given to each member, consequently each member looked at the evidence, not at the meeting, but considered it in advance. He explained that prior to the meeting the NICE technical team, assessment team and the committee chair have discussions about what evidence will be discussed in the committee meeting. MSD's RWE evidence was considered in the pre-meetings but was not thought to be important enough to discuss in the full appraisal committee meeting.

81. Claire Grant stated that if you consider the same end point as used in the NMA there was no clinically-meaningful difference between molnupiravir and competing medications. She stated that the competing product was deemed to be more efficacious on the basis of COVID-related hospitalisation and death. Importantly a decision seems to have been made using RWE but looking at a different endpoint from the NMA.

82. Dionysios Ntais, for MSD, stated that there were trends in the RWE submitted by MSD. One of these studies may not be from UK, but from Italy, however it demonstrated that differences between antivirals were not significant. That is why they were confused that none of these were thought to be of any relevance to a UK population.

83. The appeal panel concluded as follows:

84. The appeal panel noted the absence of formal stakeholder evidence submissions at the start of the MTA process to help to inform the parameters of a SLR.

85. The appeal panel noted that there were concerns about the generalisability of existing RCT data, and so it should have been anticipated by NICE that RWE would play an important role in this MTA.

86. No bespoke SLR focusing on the decision problem, including the identification and critical appraisal of relevant RWE was undertaken.

87. There was no clear framework on how RWE was introduced, with some studies introduced quite late in the process without consultation or formal critical appraisal. Similarly other RWE studies were excluded without transparent rationale. The appeal panel heard from the committee how the RWE about molnupiravir was considered and found their explanation plausible. The panel were concerned, however, that their approach was insufficiently transparent and

therefore concluded that there was also procedural unfairness on this issue.

88. Consequently, the appeal panel were persuaded that NICE had failed to take adequate steps to identify relevant evidence and treated RWE inconsistently, and therefore upheld this appeal point.

MSD appeal point 1(a)7: NICE acted unfairly because the Committee unduly focused on mortality and hospitalisation rates to assess clinical benefit rates and failed to give due consideration to other outcome measures, thereby creating bias against molnupiravir.

89. Stephen Hocking, for MSD, stated that it was not clear exactly why the decision was taken to focus on these particular outcomes. He stated that the model used was adapted from a pre-existing model for reasons of time and wondered whether these outcomes were chosen because of the limitations of the existing model. He stated that as we move into an endemic phase, hospitalisation and mortality will become less common than they were. Consequently, highly powered trials are needed to capture these outcomes. He stated that in contrast to studying hospitalisation and mortality, the study of virological outcomes would put the committee in a better position to understand the impact of therapies on the disease.

90. Janet Lord, for MSD, stated that virological outcomes provide useful indication of the efficacy of therapies and insufficient consideration was given to these outcomes in this evaluation.

91. Dionysios Ntais, for MSD, stated that the current framework does not capture wider benefits such as societal value, and the ability of the NHS to return to normal operations. He stated that cost-utility should have been expanded to capture wider benefits. He stated that the evidence requested of the company was very targeted and they were not able to explain why a wider framework should have been used.

92. The appeal panel chair asked Professor Stephen O'Brien, for NICE, if the final scope requires NICE to look at hospitalisation or if the

appraisal team have some flexibility. In response to this question and in response to the comments by MSD, Professor Stephen O'Brien stated that the team had flexibility to consider anything and everything within the scope. He stated that they heard loud and clear that the most important things were avoiding people dying and avoiding overwhelming the NHS; consequently mortality and hospitalisation were considered the most important outcomes. Finally, he stated that there were lots of risks in focusing on time to recovery.

93. In response to questioning from the appeal panel chair about why declining mortality did not change the appraisal committee's approach, Professor Stephen O'Brien stated that the appraisal team were aware of this data, and it was discussed in pre-committee meetings. He said that whilst they were aware some appellants felt there were unrecognised benefits beyond hospitalisation and death, this was not influential in NICE's decision making. Finally, he explained that they did not spend a lot of time discussing this data as there was a lack of discussion time and a feeling that the committee had to be fair to all the therapies being evaluated.

94. Ross Dent, for NICE, stated that patient experts from the population being considered, the high-risk McInnes cohort, felt that hospital attendance and death were the most important outcomes.

95. Adam Brooke, for NICE, explained that virological outcomes were included when the scope was written as at the time viral load was considered a significant risk factor and a proxy for clinical outcomes. Subsequently, the consensus developed that the pathogenesis is more complicated and that immune disruption may be more important than viral load.

96. In seeking to explain why other outcomes defined in the scope did not inform the economic model, Adam Brooke stated that time to recovery meant different things in a community or hospital setting. He explained that one is recovery in terms of leaving the hospital, and the

other is the time to recovery in terms of symptom resolution, which represents a much-reduced potential for health-related quality of life benefit.

97. The appeal panel chair asked if the scope was too ambitious resulting in NICE having to take pragmatic decisions to focus on hard data points like death and hospitalisation. He asked whether factors such as transmissibility or impact on other aspects of the health service should have been considered given that the scope included COVID in the community. Adam Brooke stated that transmissibility would require an entirely different model. He also stated that it was impossible to consider which outcomes informed the economic model without considering the concept of proportionality. He asked rhetorically whether four days of symptom resolution resulting from the use of molnupiravir was even worth modelling?

98. When asked whether decisions were taken in pre-meeting briefings, Professor Stephen O'Brien stated that he makes a point of ensuring the committee can discuss whatever they want in the pre-meeting briefing. He explained that the fact that something was difficult was not necessarily the reason they did not do something. He stated that societal benefit and time to recovery are very difficult to evaluate, but the reason they looked at them in less detail was because they are less important. He acknowledged that there was not much consideration of the side effects of medications in the evaluation and he would have liked to have spent more time on this. In response to direct questions from the panel he stated that decisions about the scope and the focus of the evaluation were discussed in committee meetings and stakeholders had the opportunity to comment.

99. Stephen Hocking stated that MSD are not saying that hospitalisation and death are not important outcomes, but that they are now less frequent outcomes. He said that Adam Brooke said that it would have been difficult to take these outcomes into account because it would

require an entirely different model. He argued that this seems to put the matter backwards as the existence of a model adopted for reasons of speed appears to have driven the outcomes measured.

100. The appeal panel concluded as follows:

101. The appeal panel noted that the scope of this evaluation contained 9 outcome measures including hospitalisation and mortality.

102. With the exception of hospitalisation and death, the appeal panel had not been presented with any evidence to suggest that anything more than cursory consideration was performed for some of these outcomes. For other outcomes defined in the scope no evidence was presented of any consideration having taken place.

103. The panel consider that stakeholders can reasonably expect that all of the outcomes identified as being potentially important by NICE should be considered in a fair and transparent way, but that did not happen in this case.

104. The appeal panel concluded, therefore, that there was evidence of procedural unfairness and upheld the appeal point.

Gilead appeal point 1(a)1: NICE acted unfairly because the lack of time and resource allocated to this MTA meant companies were not given the opportunity to make a full evidence submission and NICE refused Gilead's request to submit an economic model, resulting in important evidence not being considered by the Committee.

105. Gordon Lundie, for Gilead, stated that this appeal may take on more importance as it has relevance to the MTA and technology appraisal process generally. He asked rhetorically whether we are seeing the birth of a new MTA process. He stated that we have heard senior NICE officials describe the process as a significant success and a model for the future. He said that Professor Stephen O'Brien says we do not want an ad hoc and less rigorous process, but asserted that is what we have seen. He stated that the lack of a standard SLR was problematic. The justification for all of this keeps coming back to

speed, however this evaluation was taking place in an endemic, not pandemic context. He stated that speed is when accidents happen. He said that Gilead shared MSD's views about consultation and considered pulling out because the process no longer reflected the evidence and no longer gave the company the opportunity to put forward the best case for their product. He argued that when consultation was done it was cursory, and that Gilead asked for more involvement on several occasions. He concluded that the MTA was flawed. He stated that taking out the SLR, company engagement, submissions, and company models, put NICE in a position where it had to restrict how it looks at things, and there was inadequate opportunity for companies to be involved.

106. Kathryn Coville, for Gilead, stated that the company was aligned with MSD's first appeal point focusing on the need for companies to be able to present evidence supporting the best plausible case for their products. She said that a fundamental part of fair process is the right to be heard. She stated that this is embedded in the process published in the Manual. In this MTA, however, companies were not given that opportunity. She explained that Gilead disagrees with the assertion by NICE that the changes were not significant enough to compromise the ability of companies to participate. She stated that companies are entitled to expect NICE to follow processes, and that flexibility cannot override a fair process.

107. Kathryn Coville stated that paragraph 1.3.1. of the Manual always allows a company to make submissions. She referenced the provisions for an MTA in the Manual (paragraph 1.3.30; and 5.6.15), which say that the only difference to a single technology appraisal is that companies do not have to make a submission, but they always can, and it has to be taken into account. She said that in this MTA the ability of companies to submit evidence and make their case was restricted. Contrary to the provisions of the Manual and fair process, companies were restricted to a targeted evidence submission. She

stated that the impact of company submissions was limited as the EAG could only consider submissions after it developed its model. She said that the shortened time scale meant that there were only seven weeks between targeted submissions and first appraisal committee meeting.

108. Kathryn Coville stated that the company asked if they could provide a cost-effective analysis of remdesivir on two occasions. She described how NICE refused because they said Gilead could make the points later in consultation, but limited time was allowed to take these into account. She stated that NICE argued that it was not feasible given the number of technologies to review models from all companies. She argued that this refers back to lack of time and resources for this evaluation and stated that this was not an adequate reason for refusing to accept a submission from a company. She stated that this shows that the scope of MTA was too broad and too rushed, as the reasons given by NICE were not that Gilead's model would not be relevant to committee. She said that NICE's refusal to consider a model from Gilead disadvantaged the company, the NHS, and patients. She argued that if the company had submitted their own model it would have facilitated sub-group analysis of patients using high-flow and low-flow oxygen, and the company would have performed a PSA.

109. Kathryn Coville stated that important clinical trial data for remdesivir is reported in the SOLIDARITY trial. Gilead raised this early and kept on raising it, however it was only included after the second appraisal meeting. She explained that the company only learned the extent of the committee's concerns and how the SOLIDARITY trial would be treated in the FDG when it was too late to engage with it. She stated that there was a real possibility the company may have been able to help the committee reach a different conclusion if they had been able to engage sooner.

110. Kathryn Coville stated that the company raised concerns about the process from February 2022 onwards but continued to participate in the hope that NICE would adapt the process to make it fair. Consequently, Gilead is asking for a third committee meeting to address these failings.

111. In response Ross Dent, for NICE, stated that NICE considered the opportunity to make a targeted submission was sufficiently broad to allow the companies to submit whatever evidence they thought was missing. He stated that it was unclear what the prejudice was, given the additional opportunities to submit evidence. He accepted that this was not at the outset of the process as described in the Manual. He stated that the assessment report changed between the version issued for consultation and the version considered by the committee in the first appraisal committee showing that the EAG did make changes based on evidence submitted by the companies and stakeholders. He acknowledged that Gilead asked to submit a model and that NICE refused this request. He stated that the rationale, alongside logistical factors, was that NICE considered that anything that was missing or wrong with the EAG model could have been highlighted at the consultation stage.

112. In response to questioning from the appeal panel chair about the form of the invitation to make a targeted evidence submission, Ross Dent explained that a template was circulated to stakeholders with a very broad set of questions. He accepted that this was not a full submission as would usually be the case. In response to a question from the chair he acknowledged that they did not follow NICE procedures. He explained that this was to avoid duplication.

113. The appeal panel chair asked if Gilead were correct in stating that by the time they were aware of how SOLIDARITY data would be used, it was too late for them to do anything. Ross Dent said that there had

not been consultation on the committee's assessment of SOLIDARITY data.

114. Kathryn Coville stated that the company's request to submit a model should be viewed as a more effective way of commenting on the EAG's model than the targeted evidence submission. She stated that Gilead's argument is not that the EAG did not consult at all; it is that proper attention was not given, such that SOLIDARITY was not included when they raised it in July or August, and was only included after the second committee meeting in January.

115. The appeal panel concluded as follows:

116. The appeal panel recognise that it is common ground between NICE and the appellants that a full company evidence submission and submission of a company economic model was not permitted for logistical and pragmatic reasons following re-sequencing of the appraisal process and shortening of the timeframe.

117. The appeal panel recognised that these elements of the technology appraisal process were required by the Manual. The panel considered them to be important steps in the process to ensure stakeholder engagement, transparency, rigour and fairness.

118. The appeal panel did not consider an absence of time or resources to be sufficient justification to deviate from the process defined in the Manual. Furthermore, the appeal panel did not consider the targeted evidence submission or opportunity to comment on the EAG model to be sufficient mitigation for the unfairness introduced by not permitting companies to make a full evidence submission or to submit an economic model.

119. The appeal panel concluded, therefore, that there was evidence of procedural unfairness and upheld the appeal point.

Gilead appeal point 1(a)2: NICE acted unfairly because the lack of time meant that the EAG relied on pre-existing living systematic reviews and network meta-analyses which were not originally designed to address the decision problem and were not sufficiently validated, resulting in significant flaws in the information considered by the Committee.

120. Gordon Lundie, for Gilead, stated that the absence of a de novo SLR has shaped how the scope of the evaluation was determined.

121. Mirko Von Hein, for Gilead, stated that the EAG did not develop an SLR designed to address the decision problem. He said that the pre-existing SLR and NMA conducted by third parties, which the EAG relied on due to a lack of time, were not adequate. He stated that the EAG failed to validate the evidence on which their cost-effectiveness model was so heavily dependent. He argued that while Gilead appreciates that the EAG was put in a challenging position, it is still unacceptable to rely on an incomplete and unchecked review of the evidence. He suggested that to resolve this appeal point in a timely manner, a third committee meeting would give Gilead the opportunity to present evidence not previously captured.

122. Professor Matt Stevenson, for NICE, stated that the EAG agreed this approach with NICE. The living SLR used protocols, by respected groups. He stated that the appraisal team asked stakeholders about studies that had been missed and should have been included. He said that he is still not sure if anyone believes that they were missing key studies and until that happens, he is comfortable with using the existing NMA. He stated that whether or not there were process issues was an issue for NICE to consider, rather than the EAG.

123. Adam Brooke, for NICE, stated that in response to consultation, Gilead did provide an NMA, and this was used by the committee. Consequently, he was not sure what the issue was. He said that the only difference was the use of SOLIDARITY, and they took that into account. He argued that the process worked, NICE did a consultation, Gilead considered there was more evidence, and NICE used it.

124. In response Gordon Lundie stated that Gilead do not think the approach taken by NICE was comprehensive enough and if it had been, it would have identified SOLIDARITY initially. He said that when these issues were addressed a series of further errors occurred.

125. Mirko Von Hein stated that the Gilead are not criticising the living SLR and NMA. He acknowledged that it was a good piece of work done by a credible body. He stated that the company feel however that the existing NMA was not fit for purpose. He said it was not designed to address the decision problem in hand, the remit was to assess drugs within their given marketing authorisation. For example, it was not designed to look at evidence on oxygen requirement and remdesivir. He concluded that the company was treated unfairly by reliance on external evidence that was not fit for purpose.

126. Mirko Von Hein, in response to a question from the appeal panel chair, clarified that Gilead's objection was not to the use of an existing SLR, it was because the SLR did not address the right question.

127. Adam Brooke stated that he remained confused about what was said to be wrong with the SLR. He explained that Gilead had an opportunity to submit another NMA, which was accepted by the committee, referencing paragraph 3.20 of the FDG.

128. Professor Stephen O'Brien, for NICE, stated that they did pay a lot of attention to SOLIDARITY. He explained that it was a study with over 14,000 patients, conducted by the World Health Organisation (WHO) and published in the Lancet. SOLIDARITY concluded that remdesivir had no effect on ventilated patients and a small effect on non-ventilated patients. He said that the appraisal committee thought that through very carefully, and explained that using the low, mean, and high efficacy approach that the committee had adopted to deal with uncertainty, the committee felt that low efficacy was the appropriate conclusion in respect of remdesivir. He reiterated that SOLIDARITY

did play a part in the thinking of the appraisal committee and was considered as part of the MTA.

129. Leena Sathia, for Gilead, stated that the SLR did not identify the ACTT-1 data that was later submitted by the company as part of the focused evidence submission. She said that NICE wanted to conduct this evaluation aligned with the marketing authorisation for the included therapies, and for remdesivir there is a clear distinction for oxygen requirement that was not addressed because of the evidence base used.

130. Kathryn Coville, for Gilead, stated that the difficulty was that the EAG said a literature review following best practice was not possible due to time constraints, and as a consequence they had to be 'pragmatic'. She argued that because the pre-existing analysis was not designed to address the decision problem, it did not identify appropriate data. This meant that the company had to identify the data later over the course of the evaluation. She said that as the evidence was considered late in the process the company did not have the opportunity to respond to NICE's interpretation of the data. She stated that it was not fair to rush everything at the end of the process and present a conclusion; time has to be allowed for engagement.

131. Adam Brooke stated that the SLR did identify all the randomised data, however some of this data was 2 years old.

132. The appeal panel chair asked if NICE should have been more receptive to the submission of data during the abbreviated process, given that a formal evidence submission was not invited from the companies at the start of the process. Professor Stephen O'Brien responded that the committee were very receptive to both RCT, RWE and in vitro data. He argued that whilst not perfect, he did not think that NICE prejudiced any particular company in rejecting later submissions.

133. The appeal panel concluded as follows:

134. The appeal panel consider the living SLR and NMA utilised by the EAG to be a robust study performed by an internationally respected group.

135. The appeal panel consider the SLR to be an important part of determining the structure and parameters of EAG economic model; consequently weakness in the SLR may have a significant impact on the appraisal committee's final decision. The appeal panel accept that the questions over the appropriateness of the existing living SLR and NMA and the fact that it was not verified by stakeholders called into question its validity.

136. The appeal panel do not consider that a lack of time or resources are sufficient justification for the systemic unfairness that the absence of a dedicated SLR introduced.

137. The appeal panel do not consider that this unfairness was mitigated by the targeted company evidence submissions or later attempts of the appraisal committee to identify and consider relevant data.

138. The appeal panel concluded, therefore, that there was evidence of procedural unfairness and upheld the appeal point.

Gilead appeal point 1(a)3: NICE acted unfairly because cost-effectiveness estimates were not informed by a probabilistic sensitivity analysis without adequate justification, and so the Committee failed to sufficiently explore parameter uncertainty.

139. Gordon Lundie, for Gilead, explained that this point relates to absence of a probabilistic sensitivity analysis (PSA). He stated that this is core to the requirements of the Manual, and the absence of consideration of a PSA probably harms the company.

140. Mirko Von Hein, for Gilead, stated that two arguments were advanced by the EAG to justify omission of a PSA: time constraints, and the relative unimportance of PSA. He argued that time constraints do not

justify the exclusion of PSA and the EAG acknowledged that PSA would have been conducted if time allowed. He explained that PSA is a form of sensitivity analysis that is intended for cases where there are concerns around efficacy estimates. PSA would have been a valuable additional analysis to assess the uncertainty further and would have allowed the committee to investigate the implications of the parameter uncertainty it has relied upon to justify a negative recommendation for remdesivir. He concluded that a pragmatic approach would be to add PSA to the existing model and for the results to be discussed in a third committee meeting.

141. Professor Stephen O'Brien, for NICE, said with reference to Section 3.10 of the FDG that it was not true to say that they did not perform a PSA because they did not have enough time. He stated that the NICE team thought about it, did not think it was appropriate, and so did not ask the EAG to do it after the first committee meeting.

142. Professor Matt Stevenson, for NICE, stated that he was comfortable with the work that the EAG had done. He stated that the main reason that PSA was not performed is that it would have been uninformative to the committee. He explained that the problem is that the uncertainty that exists in efficacy does not apply to the decision problem, no one knew what the variables were, and to do the PSA would have given false certainty. It was much better to calculate a mean estimate having adjusted for non-linearity. He explained that the EAG also ran a low efficacy scenario and a high efficacy scenario. He stated that PSA would have mixed high and low efficacy into a melded bundle resulting in a cloud of uncertainty. In response to a direct question from the panel chair, Professor Matt Stevenson explained that the reason it was stated in the initial EAG report that PSA should be performed and then the EAG later changed its opinion was that the EAG subsequently "saw sense", realising that it would have been useless and would only confuse people.

143. The appeal panel chair pointed out that the Manual says that uncertainty is not a reason to exclude doing a PSA and sought NICE's view from a standpoint of process. In response Adam Brooke, for NICE, stated that the relevant section of the Manual is 4.7.12, “The committee's preferred cost-effectiveness estimate should be derived from a probabilistic analysis when possible unless the model is linear. If deterministic model results are used, this should be clearly justified, and the committee should take a view on if the deterministic or probabilistic estimates are most appropriate.” He argued that the committee followed this guidance, as documented in paragraph 3.10 of the FDG. He explained that the Manual was written with the idea that evidence synthesis would capture uncertainty that could be used to describe distributions. He said that no evidence synthesis could achieve this in the current evaluation. He stated that PSA would not affect the committee’s conclusions and would present the uncertainty on the wrong basis.

144. The appeal panel chair asked NICE to explain the discrepancy between the EAG reports and the FDG, and to explain why the committee decided not to do a PSA. Professor Stephen O’Brien stated that this was explained in paragraph 3.10 of the FDG. He said that the committee took guidance and advice from experts who said that PSA would be problematic because of difficulties of parameterising the model.

145. Professor Rachel Elliott, for NICE, explained that at committee meetings often a mix of PSA and deterministic models are presented. She stated that in this situation all the PSA gives you is a measure of parameter uncertainty. She explained that in this evaluation they had much larger sources of uncertainty such as populations going from vaccinated to unvaccinated populations. Doing a PSA still would not have told you the extent of the real uncertainty in the models.

146. Gordon Lundie said in 10 years of involvement with NICE appraisals it is the first time he had seen NICE identify an area of uncertainty it did not want to look at. He argued that PSA is something that could have been done. He said it would have been informative and relevant to the decision problem.

147. Mirko Von Hein stated that PSA is always a good way to assess parameter uncertainty. Gilead are not trying to say that PSA would have been the solution to understand all uncertainty, however the 3-way efficacy scenario alone is not enough to understand the uncertainty, especially when high and mean efficacy scenarios were ruled out from the start.

148. The appeal panel concluded as follows:

149. The appeal panel recognised that the Manual does not mandate that NICE should perform a PSA in every technology evaluation, and recognised that there may be circumstances in which it is either impractical or uninformative.

150. The appeal panel believed, however, that there is a reasonable expectation that when PSA is not performed, the justification for this should be clear and transparent.

151. The appeal panel did not consider lack of time to be sufficient justification for not performing a PSA.

152. Following the discussion of this appeal point in the hearing the panel were persuaded that the committee did sufficiently explore parameter uncertainty, and so the appeal panel were not persuaded that there was evidence of procedural unfairness.

153. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness on this issue and dismissed the appeal point.

154. During the appeal hearing, it became clear that stakeholders did not feel that they had enough information on why PSA was not performed. While the appeal panel did not uphold the appeal point, the appeal panel invite the committee to revisit the FDG to provide further explanation why they did not perform PSA in the context of paragraphs 4.7.12, 4.7.13 and 6.3.3 of the Manual.

Gilead appeal point 1(a)6: NICE acted unfairly because the Committee has not given adequate reasons for why the population requiring "low-flow oxygen" was not considered as a potential subgroup.

155. Gordon Lundie, for Gilead, stated that evidence relating to this patient group was not properly considered. He stated that Gilead raised concerns consistently throughout the evaluation.

156. Leena Sathia, for Gilead, stated that the committee had not given adequate reasons for not addressing the distinction between patients with severe COVID-19 on low-flow oxygen and those on high-flow oxygen. She explained that the remdesivir marketing authorisation and guidance distinguishes clearly between these groups. The low-flow population is important and failure to segment the population for analysis does not reflect clinical practice, or the marketing authorisation. She argued that patients with severe COVID-19 can have prolonged viral replication for up to 4 weeks, and that antiviral intervention is a critically important component, especially for immunocompromised patients. She said that failure to recommend any antiviral for hospitalised patients creates a treatment gap leading to crisis in care, postcode lottery, and inequitable treatment. She said that the cost-effectiveness may have been different if this readily defined sub-group had been examined. She stated that Gilead raised concerns during scoping, the assessment report, targeted submission, and appraisal consultation document. If the committee felt sub-group analysis was not necessary, it should have given adequate reasons. She noted that the EAG report says they only considered one subgroup for time reasons. She argued that the

committee has not considered a sub-group that they should have considered. She noted that Professor Stephen O'Brien has stated that NICE's aims were to avoid people dying and to ensure the cost-effective use of NHS resources. She concluded by stating that the use of remdesivir in low-flow patients achieves both of those aims and therefore Gilead requested a third committee meeting to consider this subgroup.

157. Professor Stephen O'Brien, for NICE, stated that whilst Gilead says it is clear that there is benefit in patients requiring low-flow oxygen, he believes that there is uncertainty. He said that in the SOLIDARITY trial there was a non-statistically significant 1.1% absolute difference in mortality between all patients assigned to remdesivir and those who were not. Therefore, he concluded there may be some benefit of remdesivir in this sub-group, but it was not clear. He stated that NICE did consider the low-flow oxygen sub-group, including during scoping, however this was not explained well in the FDG.

158. Adam Brooke, for NICE, stated that the full marketing authorisation for remdesivir was the starting point for committee discussion. He explained that the committee did consider that potentially remdesivir could have different efficacy in different subgroups and there could have been more explanation of this in the FDG. There was only reference to expert opinion rather than a committee decision in paragraph 3.30 of the FDG, and the discussion of generalisability does apply but is not directly linked. He argued that the evaluation followed process, looking at the NMA submitted and discussed at committee. He stated that SOLIDARITY was not split by low and high-flow subgroups and that this was a huge part of the analysis. He argued that the model did have functionality to consider different oxygen groups at baseline. He said that the company had an economic model and the opportunity to submit analysis at consultation, and it was not clear why they did not do so.

159. The appeal panel chair asked Professor Stephen O'Brien why he felt that the low-flow oxygen population was poorly defined when the NHS clinical commissioning policy specifically identified low-flow oxygen as a decision point in management. In response Professor Stephen O'Brien stated that it was an area of uncertainty as it was a much softer definition. He asked whether, for example, the requirement for oxygen was the same for different patients, under different doctors and teams. He said that in terms of decision-making, the appraisal committee did not see sufficiently robust evidence to make a decision specifically in relation to that subgroup.

160. Adam Brooke stated that oxygen requirements are not really split by low and high-flow in much of the guidance, but they are split into groups that require oxygen, those that require non-invasive ventilation, and those that require ventilation. He stated that the vast majority of analyses, for example, SOLIDARITY, do not split low and high-flow oxygen cohorts. He said that oxygen use guidelines and practice around the world are very different. He stated that there are lots of reasons why it is difficult to take the ACTT-1 low-flow oxygen subgroup at face value. Finally, he acknowledged that this was discussed during the evaluation but not covered in enough detail in the FDG.

161. Leena Sathia stated low-flow oxygen is well defined and the general consensus accepted and immediately recognised by most practicing clinicians is that low-flow is simple oxygenation up to 15 litres per minute. She said that the distinction between low and high-flow oxygen therapy is made in most international guidance. Further, she said that ACTT-1 showed significant mortality benefits in patients on low-flow oxygen.

162. Adam Brooke stated that the committee accepted that there is a clinical rationale for why low-flow oxygen use potentially could be a relevant subgroup in terms of the natural course of the disease. He

said that they recognised that there was a viral phase before the inflammatory phase, however they were concerned that oxygen use was a poor proxy for the likelihood that antiviral therapy would work.

163. Adam Brooke was asked by the appeal panel chair why the ACTT-1 trial, which Gilead had argued represented compelling evidence of the efficacy of remdesivir in this subgroup, was not more central to the appraisal committee's decision making. He replied that ACTT-1 was subject to the same problems of generalisability that the committee encountered throughout the evaluation. He stated that it was performed very early in the pandemic and best care had evolved significantly since then. Finally, he said that there were few events in ACTT-1, despite being clinically significant, and so it was not heavily weighted in the NMA.

164. Mirko Von Hein, for Gilead, stated that it was important to remember that the company were not permitted to submit an economic model. He said that Adam Brooke had said that the EAG economic model allowed consideration of a low-flow population. He disagreed that the EAG model allowed this, allowing only sub-group analysis for oxygenation and no oxygenation. He acknowledged that the EAG model allowed for ordinal scales, and it would have been possible to amend it to account for oxygen consumption, however he explained that Gilead were discouraged from providing their own economic modelling or amending the EAG model.

165. Professor Stephen O'Brien stated that Gilead did not submit data and so the appraisal committee did not see sufficiently robust data to allow them to make a decision in the low-flow oxygen subgroup.

166. Leena Sathia stated that the company highlighted a number of RWE studies including Garibaldi et al, Motsafari et al, and Gressons et al. They clearly demonstrated remdesivir having a mortality benefit in the low-flow oxygen cohort. She stated that Gilead also offered other

significant supporting information across all variants of concern after the second appraisal committee meeting.

167. The appeal panel concluded as follows:

168. The appeal panel were not persuaded that it was difficult to define what low-flow oxygen treatment constituted.

169. The appeal panel noted that this sub-group is recognised in clinical guidelines and in the remdesivir marketing authorisation.

170. The appeal panel were persuaded that the cohort of patients who require treatment with low-flow oxygen may represent a clinically important cohort, and understood the biological rationale for why remdesivir may be more effective in this patient population.

171. The appeal panel recognised that this cohort were consistently identified by Gilead as being a clinically important sub-group.

172. In light of this, the appeal panel would have expected to see a clear explanation of why the population requiring “low-flow” oxygen was not considered a potential sub-group, and agreed that the panel had not provided that. The appeal panel concluded, therefore, that there was evidence of procedural unfairness and upheld the appeal point.

Gilead appeal point 1(a)8: NICE acted unfairly because it treated Gilead unfairly compared to another stakeholder company by refusing to consider new data that could potentially change the Committee’s final conclusions.

173. Gilead appeal point 1(a)8 was heard together with AZ appeal point 1(a)3 and consequently the oral evidence submitted to the hearing by the appellants and representatives of NICE are summarised for both appeal points in the following paragraphs.

174. Kathryn Coville, for Gilead, stated that companies should be treated equally with respect to the cut-off point for submitting new evidence. She explained that on 31 January NICE informed all stakeholders that

certain products including remdesivir and sotrovimab would not be recommended, however NICE subsequently changed its mind and said sotrovimab would be recommended. She stated that no information was given to stakeholders, however the NICE press release said sotrovimab had been recommended following "consideration of more clinical evidence and discussion with the company." She said that this suggests that NICE took account of more evidence from GSK and that consequently it changed its recommendation. She stated that, by contrast, during the same period in early February, Gilead learned about the committee's conclusions on remdesivir and concerns about generalisability. She said that no consultation was permitted at this point. She explained that Gilead had been focusing on ensuring SOLIDARITY was considered at all, and with this new information from NICE they quickly asked for the opportunity to submit further data to contextualise the SOLIDARITY trial data. She stated that Gilead's understanding was that consideration of further evidence was not permitted, which was surprising given the focus of the appraisal committee on ensuring that it was considering the most current data. She argued that if NICE had informed Gilead that it had an opportunity to submit new evidence the company would have submitted additional data. She concluded that NICE must explain what led to the change in recommendation for sotrovimab and if Gilead were unfairly treated it could be remedied in a third appraisal committee meeting, to allow consideration of all the relevant information to ensure the final guidance is up to date.

175. Daniel Squirrell, for AZ, in reference to paragraph 5.7.66 and 5.7.67 of the Manual, stated that the evidence should be made available to all stakeholders. He stated that this has not been the case in this evaluation. He explained that AZ remain unclear as to the conversations and deliberations that took place in the second appraisal committee meeting that led to a negative recommendation for sotrovimab and the subsequent conversations and deliberations that reversed that position. He stated that clarity and transparency is

essential for them to understand how NICE will perform MTAs in the future and such clarity is required in the Manual.

176. Ross Dent, for NICE, explained that no additional evidence was accepted from GSK or considered by the committee following the second appraisal committee meeting. He stated that the committee came out of the meeting with a set of clear assumptions that resulted in sotrovimab not being considered cost-effective at that stage. He explained that the Manual provides for additional conversations with manufacturers and the opportunity to make a change to the commercial arrangement if the company accepts assumptions, and this is what happened in this case. He stated that in contrast, following the second appraisal committee meeting, NICE did not have a set of assumptions that would have meant a change in commercial arrangements by Gilead or AZ would have changed the committee's decision, and so these conversations were not initiated with Gilead or AZ. He stated that this process is described in the Manual, paragraphs 5.38 and 5.39.

177. Helen Knight, for NICE, stated that where possible, NICE will aim to facilitate access to treatments when there is an opportunity to do so, and this happens in the majority of evaluations.

178. In response to a question from the panel, Ross Dent stated that the press release is separate from the FDG. He explained that registered stakeholders receive a committee outcome email that the outside world does not receive. He stated that he thinks the confusion has arisen from the fact the press release does not say 'following additional clinical information received *in response to consultation*' and so gives the impression of referring to new clinical information provided after the second appraisal committee meeting. He stated that the new data referred to is the data considered at the second appraisal committee meeting that had been submitted following

receipt of draft guidance. He clarified that the changed decision referred to is the change in decision from the draft guidance.

179. Helen Knight stated that the press release is not appealable. She stated that NICE gave several opportunities for stakeholders to provide new information. She said that this is not the same as having an endless process of having to consult at every stage, which is why they have looked to develop a rapid update. She stated that NICE cannot keep delaying the publication of final guidance.

180. Professor Stephen O'Brien, for NICE, stated that shortly before the second appraisal committee meeting evidence emerged about the effector functions of sotrovimab which was not seen for other neutralising monoclonal antibodies. He stated that the appraisal committee thought that the evidence that sotrovimab retained some efficacy, while other monoclonal antibodies did not, was robust and convincing.

181. Ross Dent explained that a week before the second appraisal committee meeting NICE had a company briefing session to discuss the logistics of the meeting, the work done of the in vitro data expert advisory group (IVAG), and the data that the committee would consider. He stated that NICE, recognising it was late in the process to inform companies about the IVAG, offered them the opportunity to highlight any in vitro studies that they thought were missing and that the committee should consider. He stated that this is why the committee accepted GSK data at this stage.

182. Daniel Squirrell stated that the companies had not received the IVAG report at the time of the meeting described prior to the second appraisal committee meeting.

183. The appeal panel concluded as follows:

184. The appeal panel have not identified any evidence in the committee papers or during oral evidence submission that sotrovimab was

treated preferentially during the evaluation. Specifically, there is no evidence that additional clinical data relating to sotrovimab was considered, or further consultation about clinical efficacy occurred.

185. The appeal panel recognise that the framework for negotiation of cost discounts to facilitate approval for use in the NHS is described in NICE's processes, and is a routine element of the technology appraisal process.

186. The press statement released by NICE following negotiation of a commercial medicines access agreement to allow approval of sotrovimab for use in the NHS was misleading, however this lies outside of the remit of the appeal panel.

187. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness and dismissed the appeal point.

Gilead appeal point 1(a)10: NICE acted unfairly because the Committee's exclusion of treatment effects for hospital time to discharge data for remdesivir is unfair because these treatment effects were reflected in the base-case ICER results for tocilizumab.

188. Gordon Lundie, for Gilead, stated that companies have been treated differently and evidence from Gilead was not treated in the same way as that of other companies.

189. Mirko Von Hein, for Gilead, stated that the EAG initially did not consider time to discharge (TTD) data because it was not identified in the SLR and included in the NMA. The fact that favourable results derived from an analysis of 1000 patients from the ACTT-1 trial was not included in the initial analysis, highlights shortcomings of the MTA process. He said that the EAG partially rectified their error and presented incremental cost effectiveness ratios (ICERs) including time to discharge from ACTT-1, however this was not the base case. He stated that the committee said it was uncertain about treatment benefit in the endemic setting. He said that paragraph 3.23 of the FDG implies that the committee's preferred assumption is to remove

TTD for all drugs, including tocilizumab, however the base case for tocilizumab still applied TTD data. He concluded that this inconsistency in approach was unfair and unjustified, and the committee should clarify its assumptions and treat all companies equally.

190. Professor Stephen O'Brien, for NICE, stated that this is a misunderstanding, and the FDG should have been written more clearly. He explained that in paragraph 3.29 and 3.30 of the FDG the committee did not make a distinction for difference in TTD. He stated that as the appraisal committee were not convinced about the data relating to TTD, they applied a hazard ratio of 1, and so the ICERs were calculated with the same TTD data for all treatments. He stated that the committee do not think that they have been unfair but perhaps could have written that more clearly in the FDG.

191. Mirko Von Hein stated that in the committee papers from the final appraisal meeting the ICER is disclosed for tocilizumab, and if compared against the economic model, the TTD data was still incorporated in the base case results, whereas for remdesivir it was discarded.

192. Ross Dent, for NICE, responded by explaining that the company cannot know the ICERs for tocilizumab as a confidential discount was applied and so only a range was disclosed. Gilead therefore cannot conclude that tocilizumab was handled differently from remdesivir as they do not have the data to do it.

193. The appeal panel concluded as follows:

194. The appeal panel were not presented with any documentary evidence or oral evidence during the hearing that the committee treated remdesivir and tocilizumab differently. Specifically, the panel were not convinced that there was evidence that they were treated differently

with respect to how time to discharge data informed the economic modelling.

195. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness and dismissed the appeal point.

AZ appeal point 1(a)1: NICE acted unfairly because the development and use of the framework proposed by the In Vitro Advisory Group as a basis for the recommendations by the Appraisal Committee lacks transparency, was not subject to consultation and is inconsistent.

196. Daniel Squirrell, for AZ, stated that the development of the IVAG framework lacked transparency, was not consulted upon, and its findings were applied inconsistently. He stated that during the first committee meeting there were some discussions about the generalisability of clinical trial data, as newer variants of COVID-19 were emerging, and some in vitro data showed loss of efficacy. He stated that NICE had never considered in vitro data before, and it does not appear in its processes. He argued that rather than go straight to FDG, conclusions should have been consulted upon, drawing the hearing's attention to paragraph 5.7.57 of the Manual which states that, "when stakeholders submit comments that lead to a substantial revision of the committee's previous decision, involving a significant change in the recommendations, discussions or the evidence base, NICE and the chair of the committee will decide whether it is necessary to repeat the draft guidance consultation." He stated that the requirement for a second consultation is greater when NICE itself has acquired new evidence, that does not sit within existing frameworks, and NICE has used this as a fundamental basis for its conclusions. He stated that this is particularly important as the IVAG report does not reach firm conclusions how it should be used, simply stating that RCTs remain the gold standard, there was no validated tool for appraising in vitro data, and interpretation of in vitro data may be challenging.

197. Daniel Squirrell stated that AZ did engage with consultation and provide RWE. For other monoclonal antibodies there appears to be RWE that shows clinical efficacy is maintained. He stated that this is also the case for tixagevimab and cilgavimab and AZ provided some evidence that demonstrates clinical efficacy may be maintained for some variants. He stated that the committee concluded that in vitro evidence for sotrovimab is ambiguous and therefore efficacy is uncertain, nevertheless they calculated an ICER and made determinations on cost effectiveness, even though the FDG does not provide any clarity on how the IVAG data was used to produce ICERs.

198. Daniel Squirrell said that paragraph 3.12 of the FDG described in detail how the in vitro data was used to inform the cost-effectiveness of sotrovimab, however there is no information about how in vitro data has been applied for tixagevimab and cilgavimab. Finally, he expressed concern that although committee members have access to the entirety of responses received in consultation, if it is not actually put front and centre on the slides there is an incredibly low likelihood that some of this data would be discussed in committee.

199. Professor Stephen O'Brien, for NICE, stated that it was an unprecedented situation with the disease changing over the course of the evaluation. He stated that it was essential to consider in vitro data. He argued that NICE did a good job in how it gathered expertise; NICE convened a panel of the best experts in the country in this area; they met several times in December, had a thoughtful discussion, and came up with the framework. He stated that the appraisal committee would have been criticised much more if they had not done that. He stated that the data that came into the second committee meeting were all in the public domain, all high quality from reputable groups, representing a range of scientific inputs and opinions. He stated that the committee did not feel it was a piece of work that required consultation, and in consultation AZ did not disagree with the

conclusions from that process that tixagevimab and cilgavimab seemed to be less effective in neutralising Omicron variants. Professor Stephen O'Brien stated the appraisal committee were aware of a recently published paper at the time of the second meeting. He stated that it appeared to represent robust scientific evidence that sotrovimab had a separate effector function, consequently the committee reached the conclusion that tixagevimab and cilgavimab was considerably less effective against Omicron variants than sotrovimab.

200. In response to a question from the panel about the need for consultation on the work of IVAG, Professor Stephen O'Brien stated that they did not spring the information on stakeholders out of the blue as the scientific papers considered by IVAG were publicly available. He stated that he would have expected the company to know about them.

201. Ross Dent, for NICE, explained that ideally, some other group, somewhere in the world, would already have done this work, however in the circumstances NICE had to step in and do it. He stated that if another regulator had done it, or if NICE had commissioned the Decision Support Unit to do it, they would not have consulted on it. He agreed that the IVAG report was completed late in the appraisal process. He explained that the appraisal committee get the committee documents earlier than other stakeholders. He stated that the IVAG report was only finalised in early January so there was not much delay in sharing it with stakeholders. He stated that whilst the company say that the report is not externally validated, he is not sure who would do that, if you have the best experts in the UK developing it.

202. Daniel Squirrell stated that AZ agreed with the need to consider in vitro data. He stated that this will be an ongoing issue and a framework will need to be agreed for the future. He stated that the

problem is that the IVAG report does not provide any quantitative direction or conclusions on how to use in vitro data. If there is a partial loss of neutralisation, the IVAG report says essentially that they do not know what the implications are. He stated that there is room for more clarity and transparency on how in vitro data should inform decision-making. He stated that we know the report has been used for other evaluations and will be used in future. He argued that it would be fair to send it to stakeholders for consultation as whilst they were aware of the scientific papers that the IVAG group drew on to make their recommendations, they were not aware of the framework that NICE proposed to use to consider these papers.

203. The appeal panel chair asked if sotrovimab had been treated differently from other monoclonal antibodies as the in vitro data was interpreted differently and the administration costs were substantially reduced. Adam Brooke, for NICE, said in response that the differences were consistent with the IVAG framework. He stated that the IVAG were a lot more certain about how to evaluate therapies with no neutralisation activity such as tixagevimab and cilgavimab. He explained that sotrovimab was an outlier with partial neutralisation activity, so the committee had to work out how to apply partial neutralisation and compare it with RWE. He stated that the committee were aware that RWE could not be used to establish a causal relationship, but it would have been expected that RWE would have shown some evidence of reduced efficacy of sotrovimab over the course of the pandemic as mutations emerged. He stated that this was not seen for sotrovimab unlike other monoclonal antibody therapies, suggesting that it maintained efficacy against more recent variants.

204. Ross Dent stated that decisions on whether or not to undertake consultation are taken by NICE centrally, rather than the committee specifically, although they are sometimes taken in discussion with the committee chair. On this occasion NICE did discuss whether to have

another consultation or move forward with the final guidance and the NICE executive confirmed that they should be issued.

205. Professor Stephen O'Brien stated that he accepted that there was only one paper relating to sotrovimab and therefore this introduced significant uncertainty. He stated that the committee felt, ideally, they should have more data, however, that the science in this single study was well conducted. Professor Stephen O'Brien agreed that there was a lot of uncertainty, and that the committee did not implement the IVAG findings in a very sophisticated way. He explained that the committee were left with low, mean, and high-efficacy groups, and whilst there was a lot of uncertainty, they felt the data with sotrovimab "just edged it".

206. Daniel Squirrell stated that the company's intention was not to overturn a decision for sotrovimab. He said that AZ accepted that no neutralisation means no efficacy, however it is less clear for the middle ground where there is some neutralisation. It appeared that NICE had found a way to use data for sotrovimab to inform decision-making, but AZ do not know how this was applied for tixagevimab and cilgavimab. Tixagevimab and cilgavimab had significant loss of neutralisation but retained it for 14% of variants. Sotrovimab similarly had a loss of neutralisation. He stated that the company were not arguing that in vitro data should not inform decision making, however there needs to be absolute clarity about how NICE is going to use data to inform decision-making and generate an ICER. He stated that this is important as it is impossible to see how the IVAG framework will be used in the future.

207. Helen Knight, for NICE, stated that by commissioning the IVAG, NICE did something that it probably was not formally responsible for doing. She explained that they had seen similar work done by regulators in other countries, and felt it was necessary. She said that the team are proud of the work they have done. She stated that she does not know

if any regulator would have consulted on it. She argued that the right experts were in the room to allow the committee to make the necessary judgements, and the IVAG report was not something the committee could ignore. The decision NICE made is whether consultation could lead to a different outcome. She expressed concern that in the context of the rapid update process that NICE are considering, this will be difficult if they must constantly consult on how they interpret things. She stated that NICE were trying to get treatment options to patients quickly.

208. Oonagh McGill, for AZ, stated that the appeal process helps to provide a little more clarity and gives the company a better understanding of what they can bring to NICE to assist with decision making.

209. The appeal panel concluded as follows:

210. The appeal panel accept that there was a need, and a clear rationale to develop a process for the consideration of in vitro data.

211. The appeal panel consider it laudable that NICE recognised the need for the IVAG. The appeal panel agrees with NICE that the work was performed well.

212. The appeal panel consider the findings of the IVAG to be material to the conclusions that were then drawn by the appraisal committee, as significant decisions were made based on the data provided by IVAG. But this also represented a risk: for example, the panel were concerned that a single paper claiming a differential benefit of sotrovimab was given significant weight without the opportunity for scientific challenge.

213. The appeal panel note, however, that this was an entirely novel process. The panel are concerned that the data was presented to the companies without opportunity to reflect on it, or even properly digest

it, let alone take a different view as to how it should be handled. This appears to the panel to be manifestly unfair.

214. The appeal panel do not accept the argument that as the data considered by IVAG was publicly available the companies should have been aware of it and therefore there was no requirement to give them an opportunity to reflect and comment upon the conclusions drawn by the committee on the basis of IVAG's work.

215. The appeal panel concluded, therefore, that there was evidence of procedural unfairness and upheld the appeal point.

AZ appeal point 1(a)2: NICE acted unfairly because the ICERs calculated by the Committee and relied upon for its conclusion that Evusheld is not cost effective have not been disclosed.

216. Daniel Squirrell, for AZ, stated that the FDG says ICERs have been calculated, and that they could not be reported because of commercial confidentiality. He stated that it says there is considerable uncertainty but despite this, it suggests that NICE has been able to calculate an ICER for tixagevimab and cilgavimab based on neutralisation data. He argued that the company need clarity on how the ICERs have been calculated and so they need to be disclosed. He said that patient access scheme ICERs have been presented and so could be presented here, and there should have been a discussion with AZ on how they could have been presented.

217. Adam Brooke, for NICE, stated that the committee felt that the efficacy of tixagevimab and cilgavimab was even worse than the low efficacy group and so made a decision that an ICER would have been uninformative. He stated that the in vitro data showed that only 14% of variants were neutralised and potentially some of those with reduced neutralisation. He asked if from a clinician perspective, if there is only a 14% chance that tixagevimab and cilgavimab would work, would a clinician find it useful? He reflected that perhaps it would have been more informative to use something like the WHO

wording, that data was now obsolete because of lack of neutralisation, and therefore it would have been meaningless to present an ICER.

218. In response to a question from the appeal panel chair, Adam Brooke confirmed that contrary to the explanation in the FDG, the ICER was not presented as it was considered uninformative rather than because of confidentiality.

219. Oonagh McGill, for AZ, stated that publication gives them the opportunity to invest in data to help NICE, once they know the framework NICE are using for decision-making.

220. Ross Dent, for NICE, stated that when he reviewed paragraph 3.28 of the FDG there is a descriptive narrative, saying that that ICERs were produced, but do not reflect the conclusions of the IVAG. He stated that it is not very clear that NICE do not have informative ICERs and agreed that some redrafting is required.

221. The appeal panel concluded as follows:

222. The appeal panel understood that the committee concluded that although they had calculated an ICER for tixagevimab and cilgavimab, that ICER was wholly uninformative because of the degree of uncertainty related to its clinical efficacy.

223. The appeal panel do not consider that in those circumstances, the committee have an obligation to disclose a non-informative ICER.

224. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness and rejected the appeal point.

225. The appeal panel, however, suggest that the FDG is amended to reflect that the ICER was not disclosed as it was felt to be uninformative owing to the level of uncertainty and not due to reasons of commercial confidentiality, as currently stated, which is not accurate.

AZ appeal point 1(a)3: NICE acted unfairly because it considered additional evidence and participated in discussions with the manufacturer of one technology following the second Appraisal Committee Meeting but did not offer such opportunity to AstraZeneca.

226. Gilead appeal point 1(a)8 was heard together with AZ appeal point 1(a)3 and consequently the oral evidence submitted to the hearing by the appellants and representatives of NICE are summarised previously in the discussion of Gilead appeal point 1(a)8 at paragraphs 173-187.

227. The appeal panel concluded that there was no evidence of procedural unfairness and dismissed the appeal point.

228. A description of the appeal panel rationale for this decision can be found at the end of Gilead appeal point 1(a)8 (paragraph 183).

AZ appeal point 1(a)4: NICE acted unfairly because the Committee has either failed to consider or has not explained its consideration of tixagevimab and cilgavimab in the mild COVID-19 population.

229. Daniel Squirrell, for AZ, stated that the company submitted RWE that demonstrated maintained clinical efficacy to support the RCT evidence. He stated that despite this there is no consideration or discussion of tixagevimab and cilgavimab in the slides or paragraph 3.19 of the FDG. He stated that either the committee had not considered the evidence submitted in response to consultation, or had failed to be transparent and provide a summary of its conclusions.

230. Professor Stephen O'Brien, for NICE, acknowledged that the discussion the committee had about lack of compelling efficacy and lack of neutralisation in vitro could have been explained more transparently and comprehensively.

231. The appeal panel concluded as follows:

232. The appeal panel noted the acceptance by the committee chair that tixagevimab and cilgavimab was omitted from paragraph 3.17 of the

FDG. The appeal panel agreed that the committee's consideration of the evidence on this point should have been described in the FDG.

233. The appeal panel concluded, therefore, that there was evidence of procedural unfairness on this issue and upheld the appeal point.

Appeal Ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers.

MSD appeal point 1(b)1: NICE exceeded its powers as it breached its legal obligations under human rights and equalities laws.

234. MSD argued, in appeal letters during initial scrutiny, that recommending sotrovimab rather than molnupiravir disadvantages patients, many of whom have protected characteristics. They argue that sotrovimab in contrast to molnupiravir and nirmatrelvir plus ritonavir, is an intravenous therapy requiring administration in a hospital setting and can be associated with increased infection, anaphylaxis and infusion-related reaction risks.

235. MSD in appeal letters during initial scrutiny argued that this breached:

a. Article 14 of the European Convention on Human Rights (which is engaged because articles 2, 3 and 8 are also engaged) by discriminating against patients who are unable to receive nirmatrelvir plus ritonavir.

b. Section 149 of the Equality Act 2010 ("the Public Sector Equality Duty"), as NICE ought to have robustly assessed the feasibility of other treatment options that reduced inequalities of treatment.

c. Section 29 of the Equality Act 2010, on the basis that NICE should have made the reasonable adjustment of conducting a thorough assessment of molnupiravir as an alternative to nirmatrelvir plus ritonavir, including a robust assessment of all available evidence.

236. Stephen Hocking, for MSD, stated that the appeal panel might want to explore how well the committee understood that the question here is the proportionality of any adjustments that are being made to reflect the needs of vulnerable groups, and whether the committee understood the breadth and the discretion it had and should have considered exercising. He referenced paragraph 4.2.9 of the Manual that describes how the committee is charged with considering the effective use of NHS resources. He said that molnupiravir has already been purchased for use by the NHS. He argued that whilst administration costs apply, this is an unusual case in that it would not be necessary to purchase the product. He stated that the committee recognised a significant group of patients who could not take nirmatrelvir plus ritonavir and that something needed to be done for them; the difficulty is sotrovimab is a very different treatment that needs to be administered intravenously. He stated that the efficacy of sotrovimab against variants may decline, however this is less likely with an antiviral. He argued that there is a group of patients who may struggle to get to the clinical setting to receive sotrovimab such as the elderly and those with disabilities, caring responsibilities, low income, or work commitments, who are left with no treatment option. He concluded that there should have been explicit consideration of whether that group should have the option of molnupiravir to sit alongside sotrovimab as a recommended alternatives to the primary recommendation.

237. Grant Castle, for MSD, stated that the committee concluded that it was not appropriate in all cases to adjust the ICER to address these health inequalities. He said that addressing health inequalities is not just a question of flexing the ICER when duties under human rights legislation are engaged. He argued that the question for the panel is whether NICE exercised its statutory functions in a way to meaningfully address these issues. He stated that it could have done so by conducting a proper MTA in accordance with published procedures and given that it failed to do all the things it was required

to do in order to carry out a robust assessment of the evidence, it is very difficult for NICE to say it has done everything it could have done to address inequalities.

238. Janet Lord, for MSD, stated that the company is not arguing molnupiravir is more efficacious than nirmatrelvir plus ritonavir or sotrovimab. She stated that the company is arguing that patients who are ineligible for nirmatrelvir plus ritonavir and who cannot access sotrovimab are a distinct group who seem to have been forgotten and are likely to be elderly or disabled.

239. The appeal panel chair referred to advice given by the panel's legal adviser and shared with the parties to the appeal, which noted that where there is a difference in treatment between groups (and so potential discrimination) in circumstances where the decision concerns competing demands on the state's limited resources, a breach of Article 14 of the European Convention on Human Rights, incorporated into English law by the Human Rights Act 1998, is not established unless the approach adopted was "manifestly without reasonable foundation". He asked MSD's legal advisers if they were making this case. In response Stephen Hocking stated that the appeal point is brought under both the Equality Act 2010 and the Human Rights Act 1998 and that the tests are slightly different under each Act. He stated that under the Equality Act there must be justification for indirect discrimination. He explained that the Human Rights Act also protects groups falling outside those sharing 'protected characteristics' as defined in the Equality Act, for example socio-economic groups. He confirmed that MSD did consider that NICE's approach was manifestly without reasonable foundation, because there is no reason not to make drugs available that have already been procured. He argued that there is no downside; either patients get the licensed treatment, or they get no treatment at all.

240. Ross Dent, for NICE, stated that Stephen Hocking said that molnupiravir has already been purchased and therefore there is no reason not to recommend it. He stated that this cannot inform the committee's decision making as this is a decision about the future commissioning arrangements for the NHS. He explained that what has already been purchased is not relevant as NICE cannot take that into account when making future commissioning decisions that could last in perpetuity well beyond the time that the stock has been exhausted.

241. Stephen Hocking in response, asked if the appeal panel would make a finding on whether the point made by Ross Dent, that NICE could not account for drugs that were already purchased in its guidance, was correct in the context of equality law. He acknowledged that this is a novel situation, however he stated that NICE is charged with the efficient use of NHS resources.

242. Professor Stephen O'Brien, for NICE, explained that there was a need for an alternative to nirmatrelvir plus ritonavir as it is relatively contraindicated in conditions such as transplantation. He stated that the committee were very active in thinking about avoiding inequality in this case. He said that high-risk patients are likely to be using medicines that make nirmatrelvir plus ritonavir relatively contraindicated. He explained that the committee were conscious not to leave a hole for those patients. He stated that this was discussed at great length before, during and after the committee meeting, and following this discussion they did not think molnupiravir was appropriate because the committee were not convinced of its clinical effectiveness. He stated that the company contend that sotrovimab is difficult to administer because it is intravenous rather than oral, however in his clinical practice over the last 18 months he has made hundreds of phone calls to patients who cannot take nirmatrelvir plus ritonavir and he cannot think of a single occasion when sotrovimab was declined because a patient could not come to hospital. He stated

that patient groups (such as Kidney UK) welcomed sotrovimab and did not say in consultation that it would be hard to take. He stated that coming into hospital is not a big problem for this group. He concluded by saying that he refutes that NICE have created an inequality by recommending sotrovimab rather than molnupiravir, and that the committee strove to avoid that inequality.

243. Stephen Hocking said in response that experience from clinical practice over the last 2-3 years when patients were understandably anxious about COVID-19 may not be a reliable guide to how patients will access treatments in future. He argued that some patients may think to themselves that it is not worth going in for IV therapy, whereas if they have an oral alternative there would be no barrier to treatment.

244. Professor Stephen O'Brien stated that they have not heard from patient groups about the inequality contended by MSD about sotrovimab. Only the company has raised this; patient groups are broadly welcoming of sotrovimab.

245. Janet Lord stated that the patient organisations that attended the appraisal committee meetings such as Kidney Research UK, Kidney Care, and Anthony Nolan all represent patients who usually attend hospital for treatment. The populations who cannot easily come to hospital such as Age UK were not represented at the meetings. She stated that when MSD talk to clinicians this is what they are hearing.

246. Grant Castle stated that NICE commented on a number of occasions that they had not heard any concerns from the patient community about sotrovimab. He stated that you have to ask yourself when they might have raised those concerns. They were only consulted in the context of a draft recommendation focused on nirmatrelvir plus ritonavir. He explained that sotrovimab only became an issue at a very late stage, and procedures do not allow NICE to engage with the patient community at that stage. He explained that patient interest

groups could only have expressed concerns about sotrovimab on appeal, and this cannot be the way to run a health technology assessment process.

247. Stephen Hocking stated that the Medicines and Healthcare products Regulatory Agency (MHRA) considers molnupiravir efficacious and whilst NICE may reach its own view, he would question whether the finding that this drug has no clinical efficacy is open to NICE. Even if NICE thinks it has limited clinical efficacy, in patients who would otherwise have no treatment this must be of some benefit.

248. Ross Dent stated that there were three experts in the meeting, who were supportive of sotrovimab and did not raise any of the equality issues that MSD have raised today. He said that consultation generated strong preference for sotrovimab and none of the stakeholders raised any equality issues in relation to sotrovimab, or NICE would have taken them into account.

249. Helen Knight, for NICE, stated that guidance cannot go into every individual patient circumstance. If sotrovimab was not an option, individual factors can be considered. She stated that the appraisal committee have looked at clinical and cost-effectiveness, considered inequalities, then taken a proportionate approach to achieving a legitimate aim, conscious that this decision will displace healthcare funding elsewhere in the system. She concluded that if there had been potential to find molnupiravir cost-effective, the committee would have done so.

250. Janet Lord stated that there have been several RCTs evaluating the efficacy of molnupiravir. She stated that the MHRA have considered it, and the US Food and Drug Administration (FDA) have approved it. The PANORAMIC study has negatively impacted molnupiravir, and molnupiravir is being unfairly judged here.

251. The appeal panel concluded as follows:

252. The appeal panel proceeded on the basis that at least one of articles 2, 3 and 8 of the European Convention on Human Rights was engaged, and therefore considered whether the committee had breached Article 14.

253. The appeal panel understood the appellants' position was that a vulnerable sub-group of patients would not have access to effective treatment for COVID-19 because nirmatrelvir plus ritonavir was contraindicated, and sotrovimab had been approved in preference to molnupiravir because the appraisal committee considered it to be more clinically and cost-effective. As sotrovimab is an intravenous medication, and requires administration in secondary care, the appellants were concerned that patients in this group would be unable to access treatment.

254. The appraisal committee asserted that sotrovimab is a clinically effective and cost-effective medication whilst molnupiravir is not cost-effective and its clinical efficacy is more uncertain. Assumptions about the relative clinical efficacy of sotrovimab and molnupiravir were not challenged, and even implicitly accepted by MSD during the appeal hearing. All things being equal a patient may prefer to have an oral medication, unless the oral medication has reduced or limited efficacy.

255. The appraisal committee did not hear compelling oral evidence or see documentary evidence that the necessity to attend secondary care for treatment was a significant or unreasonable barrier to accessing healthcare.

256. In conclusion the appeal panel were not convinced that recommending an apparently more clinically and cost-effective medication, which did not have significant barriers to accessing it, could be considered to be manifestly without reasonable foundation.

257. Consequently, the appeal panel concluded that NICE had not breached article 14 of the ECHR.

258. In light of the committee's consideration of molnupiravir in this context, the appeal panel was satisfied that NICE had had due regard to the needs to remove or minimise disadvantage suffered by persons who share a relevant protected characteristic and to take steps to meet the needs of people with a protected characteristic that are different from those who do not. In reaching this view, the panel noted that the committee could not be said to have acted outside the scope of any reasonable public authority in the circumstances. The appeal panel therefore concluded that NICE had not breached the public sector equality duty set out in s149 of the Equality Act 2010.

259. The appeal panel also considered MSD's contention that the committee had failed to meet its duty to make reasonable adjustments under section 29(7) of the Equality Act 2010.

260. The panel agreed that many of the patients for whom nirmatrelvir plus ritonavir is contraindicated may have protected characteristics defined in the Equality Act 2010. The panel noted that the duty to make reasonable adjustments applies only in relation to disabled people. The panel noted that this might not cover all patients for whom nirmatrelvir plus ritonavir is contraindicated. Nevertheless, the panel considered all elements of the duty.

261. The panel agreed that the absence of treatment for COVID-19 for this patient group could constitute substantial disadvantage in comparison with persons who are not disabled.

262. The appraisal committee were conscious of this and recommended sotrovimab as an alternative, believing that this constituted reasonable steps to avoid the identified substantial disadvantage.

263. MSD contend that this has resulted in the necessity for these patients to access treatment for COVID-19 in a secondary care setting which

in itself constitutes substantial disadvantage, and advocate the approval of molnupiravir, an oral medication, as a reasonable step to avoid this further identified substantial disadvantage.

264. The appeal panel disagree with MSD for two reasons,

a. Firstly, the evidence from the documents and the appeal panel hearing is not compelling that accessing healthcare in a secondary health care setting constitutes a substantial disadvantage.

b. Secondly, even if it is accepted that the necessity to access healthcare in a secondary healthcare setting is a substantial disadvantage, they are not persuaded that recommending a medication with uncertain clinical effectiveness is a reasonable step to avoid the identified substantial disadvantage.

265. The appeal panel concluded, therefore, that there was no evidence that NICE has exceeded its powers by breaching its obligations under the Equality Act 2010 or the Human Rights Act 1998.

MSD appeal point 1(b)2: NICE exceeded its powers by allowing the EAG to take decisions that should have remained with the Committee.

266. MSD appeal point 1(b)2 was heard together with MSD appeal point 1(a)2 and consequently the oral evidence submitted to the hearing by the appellant and representatives of NICE are summarised previously in the discussion of MSD appeal point 1(a)2 at paragraphs 53-71.

267. The appeal panel concluded as follows:

268. The appellants have argued that delegation of decision making to the EAG by the appraisal committee would result in NICE overreaching its powers.

269. The appeal panel were uncomfortable with the apparent freedom given to the EAG to “pragmatically assess where time savings can be made without impacting on the main conclusions” outlined in the first

report. The appeal panel were however unable to identify any example when decisions were made by the EAG without the knowledge, oversight, and approval of the appraisal committee.

270. The appeal panel concluded, therefore, that NICE did not overreach its powers and this appeal point is not upheld.

Gilead appeal point 1(b)1 (originally 1(a)5): NICE exceeded its powers as the Committee did not conduct a thorough assessment of treatments for children with severe COVID-19 and the resulting failure to recommend any treatment for children with severe COVID-19 is unfair and discriminatory.

271. Kathryn Coville, for Gilead, stated that NICE had not complied with its legal obligations to consider the position of children. She explained that remdesivir is the only licensed treatment for children with severe COVID-19. In October 2022, the licence was extended to children over 4 weeks of age with severe COVID-19. She said that NICE's decision had two implications. Firstly, there were limited treatment options for children and therefore they have a different degree of clinical need. She stated that NICE has a legal obligation to take account of the degree of need. Secondly, if remdesivir is not recommended, then this is unlawful indirect discrimination against children unless it is a proportionate means of achieving a legitimate aim.

272. Kathryn Coville stated that NICE had an obligation to have due regard to the need to remove or minimise disadvantage suffered by persons who share a relevant protected characteristic and to take steps to meet the needs of people with a protected characteristic that are different from those who do not. She said that NICE should have considered the specific situation of children with COVID-19 and made a well-informed view on cost-effectiveness. She argued that before making a negative recommendation, NICE should have considered whether this was a proportionate means of achieving a legitimate aim, and NICE should have looked at whether less intrusive options could

achieve that aim. She said that the committee did not do this. She argued that the committee did not consider the different clinical needs of children, or cost-effectiveness for children. They seemed to assume that if treatment was not cost-effective for adults, it would not be cost-effective for children. She stated that the committee did not calculate any ICERs for children or consider if its approach to uncertainty in remdesivir was appropriate. This potentially leaves no option but to treat children with severe COVID-19 with non-licensed therapies. She concluded that the committee did not explain how this indirect discrimination was a proportionate means of achieving a legitimate aim, and whether the impact on children with severe COVID-19 was a reasonable price to pay to achieve a cost-effective recommendation. Consequently, Gilead would like the committee to give further consideration to the position of children with severe COVID-19 in compliance with equalities legislation.

273. Professor Stephen O'Brien, for NICE, said that he had enormous sympathy for this point. He stated that following the first meeting the appraisal committee felt that they had not sufficiently considered treatment in children. He explained that the committee listened to feedback received in consultation and discussed it further in the second appraisal committee meeting. Dr Elizabeth Whittaker was invited to attend the second meeting to help the committee understand the issues relating to treatment of COVID-19 in children. He said that the situation regarding children was difficult as the evidence base on clinical effectiveness in children is sparse as severe COVID-19 in children is rare. He explained that NICE did not formulate ICERs in this group because there was so much uncertainty it would not have been helpful to decision makers. He concluded that although the committee carefully considered this patient group the committee felt that they did not have sufficient evidence to make conclusions about clinical and cost-effectiveness.

274. In response to a question from the appeal panel chair Professor Stephen O'Brien stated that the appraisal committee were specifically tasked with making recommendations on the basis of clinical and cost-effectiveness, and he agreed that "equality legislation does not trump efficacy".

275. Leena Sathia, for Gilead, stated that to get a licence extension for use in paediatrics data was submitted to the MHRA that they considered enough to show clinical efficacy. She conceded that she did not think that Gilead specifically highlighted paediatric data in the company's limited evidence submission.

276. Ross Dent, for NICE, stated the committee recognised that at the first meeting it had not appropriately considered children, in part because the licence extension came very shortly before the October meeting. He explained that NICE tried to address this by inviting a paediatric expert. Treatment of children was discussed, including compassionate use. He said that there was general agreement that the quality of evidence was not high, including single-arm studies, which the committee felt should be interpreted with caution. He explained that the committee did make the assumption that stronger evidence for adults would apply. He said that this might be an optimistic assumption. He concluded that in mild COVID-19, the ICERs for adults were very high, and although the committee were minded to have some flexibility, ICERs over £100,000 were felt to be excessive. For severe COVID-19 the conclusion that evidence was too uncertain from studies in adults was applied to children.

277. Kathryn Coville stated that the question for the appeal panel is whether NICE has done enough to meet obligations under equalities legislation. In conclusion she asked the panel to consider whether it was sufficient that the committee did not look at real ICERs.

278. Helen Knight, for NICE, stated that she hoped that NICE have demonstrated today and, in the documents, that they carefully

considered this patient population. She stated that NICE invited a paediatric expert to the appraisal committee meeting and recognised that a treatment option should always be available. She stated, however, that they have to look at the remit of NICE, to evaluate both clinical and cost-effectiveness. She stated that they did not have ICERs for children but did carefully consider a recommendation for children separately. She stated that none of the stakeholders provided any information on how they could generate ICERs for children. She stated that the committee did carefully consider treatment of COVID-19 in children, acknowledging remdesivir was the only licenced treatment. She stated that she did not know what more the committee could have done. She stated that the committee took all the evidence and deliberated on whether they could make a recommendation for children, noting children had unmet clinical need, however this did not mean that NICE could recommend a treatment that was not cost-effective in clinical practice.

279. The appeal panel concluded as follows:

280. The appeal panel was not persuaded that the committee's approach was manifestly without reasonable foundation, and accordingly did not find any breach of Article 14 ECHR.

281. As age is a protected characteristic the appeal panel recognised that section 29 of the Equalities Act 2010 is engaged.

282. The panel was satisfied that the committee had considered children as a distinct and separate patient population extensively, and therefore had due regard to the needs to remove or minimise disadvantage suffered by persons who share a relevant protected characteristic and to take steps to meet the needs of people with a protected characteristic that are different from those who do not.

283. The appeal panel recognised NICE's legitimate aim of maximising health benefits for available NHS resources by recommending clinically and cost-effective healthcare interventions.

284. The appeal panel recognised that the decision not to recommend remdesivir for people with severe COVID-19 because its clinical and cost-effectiveness is uncertain is consistent with NICE's legitimate aim.

285. The application of this legitimate aim in this case, however places children with severe COVID-19 at a particular disadvantage, because unlike adults they cannot access any other licenced treatments. The appeal panel considered this to be indirect discrimination.

286. The appeal panel were unconvinced that in this case the disadvantage was justified as a proportionate means of achieving NICE's legitimate aim, taking account of the rarity of COVID-19 in children and consequently the minimal burden that a positive recommendation for remdesivir may have on overall NHS resource utilisation.

287. The appeal panel therefore upheld this appeal point.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

MSD appeal point 2.2: The Appraisal Committee's administration cost assumptions for molnupiravir and nirmatrelvir plus ritonavir are unreasonable.

288. Stephen Hocking, for MSD, acknowledged that administration costs did not drive the recommendation. He stated, however, that should the analysis be redone in the future then it will be important to MSD that this will be on the basis of proper administration costs.

289. Dionysios Ntais, for MSD, stated that clinical experts argue that applying the COVID-19 Medicines Delivery Unit (CMDU) costs is inappropriate. He stated that the cost of GP consultation, patients

being prescribed and dispensed molnupiravir, and drug delivery adds up to less than one third of the cost used by the CMDU, even when adjusted for the costs associated with more intensive care for particular patient groups. He stated that throughout the appraisal MSD have provided more applicable costs.

290. Grant Castle, for MSD, stated that it was not clear to the company why the committee chose to ignore relevant representations. He stated that as we move to an endemic phase molnupiravir will increasingly be administered in primary care. He stated that MSD support the use of unit costs from the primary care manual. He stated that it is not clear why NICE ignored those views and used less appropriate estimates.

291. Professor Stephen O'Brien, for NICE, stated that although you would expect it would be very clear how much it would cost to have a GP assess a patient and send out some pills, in reality this is not clear. He stated that the cost of having hundreds of GPs and pharmacists making phone calls is more than might be anticipated. He explained that there is also an opportunity cost to the NHS of distracting people from other work, which is unmeasured. He stated that the committee now felt that the most reliable source of information on administration costs was from NHS England, however this remained surprisingly uncertain.

292. Ross Dent, for NICE, said that it was not true to say everyone said that the figures for administration costs were wrong. He stated that NHS England said they thought the figures were correct. He explained that at the committee meeting it was not clear what the delivery model for the drugs was, and that this remains the case now. Ross Dent drew the hearing's attention to paragraph 3.26 of the FDG which describes how the committee considered a range of administration costs in their decision making, in light of uncertainty. As the committee were not able to identify with absolute accuracy

what the administration costs would be in the future, they considered a range of scenarios, particularly focusing on those where it could potentially change the decision.

293. In response to a question from the appeal panel chair, Ross Dent stated that MSD had taken a view on how the drug would be delivered, however this is a choice for health care providers. He stated that the committee did not hear anything from NHS England suggesting that they thought the information they had given to NICE was out of date, or that plans were in place to deliver the drug according to the model suggested by MSD. He stated that despite this, the committee looked at different costs, including lower costs that would be more aligned with primary care delivery models, as described in paragraph 3.28 of the FDG. He stated, however, that this was not material to the committee decision-making as the uncertainty relating to molnupiravir mainly related to its clinical effectiveness.

294. Dionysios Ntais stated that the company had not seen any analysis of lower administration costs being applied. He stated that the analysis was based on a flawed evidence synthesis and the drug's perceived lack of effectiveness.

295. Grant Castle stated that NICE appears to have taken administration costs from the pandemic phase, when the drug was administered in secondary care, from the CMDU (which is now being disbanded). He stated that exploration of whether these administration costs are realistic for an endemic disease was either not performed or performed in an opaque fashion. He stated that this reaches the standard of unreasonableness that would get a court interested.

296. In response to a question from the appeal panel chair about whether paragraph 3.26 of the FDG describes how alternative administration costs were considered, Grant Castle stated that his interpretation of this paragraph was that because of uncertainty about future delivery models this was not modelled.

297. Adam Brooke, for NICE, stated that the misunderstanding here appears to be because not all stakeholders are familiar with the concept of Net Monetary Benefit (NMB). He explained that NMB was used to present results according to different ICER thresholds, and these can be rearranged to allow the committee to understand the impact of different administration costs.

298. Helen Knight, for NICE, stated that she was not sure how they could have been clearer, given the time the appraisal committee spent discussing this in the meeting. She stated that the committee took all the delivery model options into account. She explained that the CMDU costs may be an overestimate, and that primary care costs may be an underestimate resulting in uncertainty. She stated that the committee considered a range of scenarios, in some circumstances administration costs had an impact on whether an intervention was cost-effective, in other circumstances administration costs did not.

299. Dionysios Ntais stated that estimates of the NMB are reliant on all of the other assumptions about the effectiveness of molnupiravir.

300. Ross Dent stated that section 3.2.8 of the FDG described how the committee were very uncertain about administration costs and so NMB was used to consider a range of administration costs, where it was potentially a driver of cost-effectiveness. He explained that the ICER for remdesivir was extremely high, and examination of the effect on administration costs on NMB did not suggest that they would make any difference to the cost-effectiveness of remdesivir. He stated that in contrast the ICER for nirmatrelvir plus ritonavir was very low, translating into a positive recommendation, so different administration costs would not make any difference. He explained that whilst the ICER for sotrovimab cannot be reported it was over £20,000 per Quality Adjusted Life Year (QALY), and was unchanged when lower administration costs were considered. He explained that when considering the population that could not take nirmatrelvir plus

ritonavir, the cost-effectiveness of sotrovimab was more marginal and administration costs did make a difference. Given that the committee were trying to address an equality issue, and given the significant uncertainty, the committee decided that it was not appropriate to make a decision to not recommend sotrovimab based on very uncertain administration costs. He stated that consequently the committee gave guidance that sotrovimab would be cost-effective only if administration costs were approximately £400.

301. In response to a question from the appeal panel chair, Ross Dent agreed that it was unclear in the FDG that the committee followed this process for all the drugs, not just sotrovimab.

302. Helen Knight stated that NICE would be happy to amend the wording of the FDG, but the documentation would be incredibly long if NICE were to write the same thing for all seven treatments. She reassured the hearing that NICE would not unfairly perform scenario analysis for selected interventions and that NICE only report analyses in the FDG that are material to decision making. In response the appeal panel chair stated NICE has an obligation to clarify things in the FDG that are unclear, and that stakeholders have a legitimate expectation that this should be performed.

303. Grant Castle stated that he did not think that this issue could be resolved by re-wording the FDG. He stated that it appears to be illogical, unreasonable, and discriminatory to assume administration costs are equivalent for intravenous and oral medications because the ICER was marginally over £20,000 per QALY.

304. Ross Dent in response stated that the committee did not reach firm assumptions on administration costs for any of the drugs, but considered a range for all of the administration costs for all drugs and reported the results where it made a difference.

305. Stephen Hocking asked why the administration cost for a treatment administered intravenously could be uncertain as the delivery model will not change. In response Ross Dent stated that the administration cost includes how patients are identified.

306. Professor Stephen O'Brien stated that administration costs are unlikely to change as patients are still going to need to come to hospital. He stated that similarly they are also unlikely to change for a tablet, as administration will still require a doctor needing to contact the patients and arguably this will take the same time for a GP and hospital specialist.

307. Ross Dent stated that the conclusion of the committee was that sotrovimab is effective when an administration cost of £400 is used. He stated that the conclusion is not that the cost of delivering an IV is the same as delivering an oral medicine. The conclusion is that sotrovimab is effective when an administration cost of £400 is used. NICE do not know the administration cost. He said that the purpose is to guide stakeholders as to the level of administration cost required to see cost effectiveness.

308. The appeal panel concluded as follows:

309. The appeal panel understood MSD's arguments about why the administration costs of molnupiravir may fall with time as it becomes more widely administered in a primary care setting. This is yet to be realised and consequently the appeal panel do not consider the base-case assumptions relating to the administration costs of molnupiravir to be unreasonable in light of the evidence submitted to NICE.

310. The appeal panel were concerned about the sensitivity analysis that was undertaken to investigate the effect of administration costs on cost-effectiveness.

311. The appeal panel did not find any justification in the documents or the oral evidence from the appeal hearing to justify plausibility of the

lower-limit for the intravenous administration costs used in the analysis.

312. The appeal panel were particularly concerned that this implausibly low figure, which is less than the cost of administering an oral medication, was used to inform the adoption of sotrovimab.

313. The appeal panel, concluded therefore, that this was unreasonable in light of the evidence submitted to NICE and upheld the appeal on this point.

MSD appeal point 2.3 (originally 1(a)5): The recommendation is unreasonable in light of the conclusions drawn from the PANORAMIC data, which were unreasonable taking into account the known limitations of the data and the weight that was applied to this data set.

314. Claire Grant, for MSD, stated that the company had several concerns relating to how PANORAMIC data was handled within the MTA. She stated that.

a. It was performed in an irrelevant population to the decision problem. Whilst PANORAMIC was performed in patients with the correct variant and vaccination status, it was performed in the wrong patient population. Only about 15-20% of patients in PANORAMIC align with the McInnes definition of high risk. This was critical when considering what effect PANORAMIC had on the living NMA that informed the economic model, where between 20,500 and 21,800 irrelevant patients were included. If considering nirmatrelvir plus ritonavir ineligible patients, then 24,900 included patients were irrelevant. Critical sensitivity analysis to understand influence of PANORAMIC on the living NMA was not performed.

b. As PANORAMIC was a large study it had a disproportionate impact despite being performed in an irrelevant population.

c. PANORAMIC data was used inconsistently across technologies. Only molnupiravir was tested in PANORAMIC and this informed baseline hospitalisation rates. However, the appraisal committee felt these hospitalisation rates were underestimates and used other estimates for competing technologies. Whilst these numbers were small, they are a significant driver of the economic model. The underestimation of hospitalisation rate in PANORAMIC supports MSD's argument that PANORAMIC was performed in the wrong population.

d. The uncertainty associated with PANORAMIC was dealt with inconsistently during the evaluation. If it is accepted that outcomes are underestimated in PANORAMIC, the starting point for the base case analysis should be the mean efficacy estimate. To adjust for the irrelevant (less-severe) patient population, the appraisal committee should have started at mean efficacy and adjust for uncertainty by moving towards the upper efficacy estimate. Moving to the low efficacy estimate makes the uncertainty even greater, and therefore does not make sense.

e. The appraisal committee relied on the wrong outcome reported in PANORAMIC and OpenSAFELY.

315. Janet Lord, for MSD, stated that the CMDU relied on the McInnes criteria to treat high risk patients, and this was supported by commissioning criteria. She stated that PANORAMIC had its own inclusion criteria, and consequently the authors say the findings may be less applicable to high-risk patients. She stated that alternative RWE evidence that supported molnupiravir appears not to have been considered because it was not UK evidence, however it was performed in comparable healthcare systems (Italy and Israel), for the same population and same variants.

316. Dionysios Ntais, for MSD, stated that the company informed NICE that this NMA would not withstand scrutiny. He stated that MSD had performed internal work to demonstrate inconsistency in baseline risk between PANORAMA and MOVe-OUT. He stated that if the SLR had taken place, full assessment of what endpoints could be synthesised would have been undertaken. He stated that despite EAG concerns about the use of different endpoints, no steps were taken to address these differences and PANORAMIC was included, with the assumption that the results were generalisable. He stated that if any adjustments were made, MSD could not identify them.

317. Professor Stephen O'Brien, for NICE, stated that PANORAMIC is a strong study. He stated that it was not an unreasonable assumption that the relative effect was similar in high-risk and lower-risk patients and so the starting point was the low efficacy scenario. He stated that there was no evidence to support a move to the mean efficacy scenario and he would refute MSD's contention that PANORAMIC should not be considered.

318. Professor Rachel Elliott, for NICE, sought to clarify that she stated that the PANORAMIC trial had hospitalisation rates that the committee felt may be considered lower than the actual hospitalisation rate in high-risk patients. She stated that at no point did she suggest that clinical effectiveness was underestimated in PANORAMIC.

319. Professor Matt Stevenson, for NICE, explained that one key consideration in different populations is whether any of the characteristics are treatment effect modifiers. He stated that he had not seen any evidence that the population characteristics in the PANORAMIC trial were treatment effect modifiers.

320. Adam Brooke, for NICE, stated none of the RCTs for molnupiravir included patients that met the McInnes criteria except PANORAMIC

which included some of these patients. He stated that PANORAMIC still represents a more generalisable population than any other RCT.

321. In response to a question from the appeal panel chair, Adam Brooke stated that there was no evidence framework to make any adjustment to the NMA to reflect the fact that PANORAMIC did not reflect the McInnes population. He stated that meta-analysis is intended to find a core treatment effect, and many clinicians questioned the value of meta-analysis because there were multiple different treatment effects.

322. Claire Grant stated that MSD thought the committee should not have dealt with the uncertainty resulting from the low-risk population by adopting the low-efficacy scenario when greater efficacy is observed in a high-risk population. She stated that the uncertainty should have driven adoption of the high-efficacy scenario. In response to a question from the appeal panel chair she stated that there was a clear trend amongst the older, more co-morbid patient population who were vaccinated, in the twenty RWE studies that MSD submitted, to support the adoption of the high-efficacy scenario.

323. Adam Brooke stated that MSD were conflating two different types of uncertainty. He stated that all of the other RCTs had population, vaccination and immunity issues, except PANORAMIC which only had population issues.

324. Professor Stephen O'Brien stated that the 20 RWE studies showing a clear trend is not statistically robust compared to a large RCT, even with all the caveats discussed. He argued therefore that it was reasonable to start at a low efficacy point.

325. In response to a question from the appeal panel about whether MSD was only interested in the high-risk subgroup, Claire Grant stated that the appeal point is wider than that. She explained that by the time of the second appraisal committee meeting the definition applied to the population was the McInnes high-risk criteria which were

fundamentally different from the PANORAMIC population. The nirmatrelvir plus ritonavir ineligible patients in the FDG were considered to be an even higher risk patient population, so the PANORAMIC population were even less generalisable to this patient population.

326. Professor Stephen O'Brien stated that PANORAMIC was much broader than McInnes which was a smaller trial. He stated that PANORAMIC enrolled patients who were not recruited into the McInnes trial. He stated that appraisal team were very aware of the difference, and how those trials had concluded.

327. Adam Brooke also stated that the scope of PANORAMIC was much broader. He explained that because of all the changes that occurred during COVID-19, the absolute risk of hospitalisation and death had fallen so much that they needed to consider subgroups at highest risk.

328. Claire Grant stated that if the hospitalisation rate was an underestimate, and they expected to see higher hospitalisation in the high-risk population, then PANORAMIC was not the right population. She asserted that if the Oxford investigators had been approached for the data cut that most closely resembled McInnes or nirmatrelvir plus ritonavir ineligible patient populations it would have been helpful.

329. Adam Brooke stated that Slide 56 from the first appraisal committee meeting showed that the results of the NMA were considered with and without the results of PANORAMIC. He also stated that although the PANORAMIC authors were not approached the study contained a subgroup analysis for immunocompromised patients, showing a non-significant trend towards worse outcomes in this high-risk group.

330. Grant Castle, for MSD, stated that the hearing has heard speculation both from MSD and NICE about the effect of PANORAMIC, and discussion about how this uncertainty may be resolved. He said that we just do not know the answer to those questions. He stated that if

NICE had performed its own SLR it could have looked at these issues, but it chose not to do that.

331. Janet Lord stated that molnupiravir is the only drug impacted by PANORAMIC which is unfair. She stated that the authors of PANORAMIC state that this is a pragmatic study. She argued that the control arm was very heterogeneous, and we do not know how many in the control arm had molnupiravir or nirmatrelvir plus ritonavir. She stated that the PANORAMIC authors state that early treatment with antivirals may prevent deterioration, yet 13% of patients received molnupiravir more than 5 days after symptoms started.

332. The appeal panel concluded as follows:

333. The appeal panel recognised the reservations that MSD have about the generalisability of the PANORAMIC trial to a higher-risk population.

334. The appeal panel recognised that the PANORAMIC data could have been used differently to inform this technology appraisal, and that there may have been advantages in alternative strategies over the one that the appraisal committee ultimately adopted.

335. Nevertheless, the appeal panel recognised the attempts that the committee made to contextualise the data and examine its generalisability. The panel considered the committee's explanation of the steps taken and were satisfied that the committee's approach was not unreasonable.

336. The appeal panel, concluded therefore, the committee’s approach to the PANORAMIC data was not unreasonable in light of the evidence submitted to NICE and rejected the appeal on this point.

MSD appeal point 2.4 (originally 1(a)6): The Appraisal Committee's blanket capping of the efficacy levels of all treatments, without due consideration of each individual case was unreasonable.

337. Dionysios Ntais, for MSD, stated that throughout the MTA the evidence for molnupiravir was evolving. He stated that depending on what outcome you are looking at, there are several studies that demonstrate efficacy of molnupiravir. He stated that despite this NICE applied a blanket cap on efficacy that is inconsistent given the number of RCTs informing relative treatment effect. Finally, he stated that there was no need to apply low blanket efficacy, and the cap cannot address the lack of a PSA.

338. Professor Stephen O'Brien, for NICE, stated that they were considering many drugs in a changing environment and therefore considered low, mean, and high-efficacy scenarios. He stated that whilst this approach was somewhat simplistic it seemed reasonable in the constantly changing environment. He disagreed that this was the same as applying a blanket cap.

339. Adam Brooke, for NICE, stated that for molnupiravir the Hazard Ratio for the mean treatment efficacy was 0.80 with an upper confidence interval of 1.15. Consequently, there was low confidence in the efficacy of molnupiravir and the low efficacy scenario only just included the median of PANORAMIC. He stated that the low efficacy result may not be that conservative if PANORAMIC gives higher confidence.

340. Dionysios Ntais stated that this method essentially creates a ceiling effect. He stated that for molnupiravir where there are 5 RCTs and so more certainty, this method is not appropriate.

341. Adam Brooke stated that the committee were fully aware of differences between evidence bases from PANORAMIC and other trials, and still believed that the range was appropriate.

342. Dionysios Ntais stated that the way that the NMA had been factored in resulted in an element of double counting or double disadvantaging molnupiravir because of the way that PANORAMIC was introduced into the NMA. He stated that this is the wrong population and should not have been done, as it dilutes the treatment effect. He stated that molnupiravir was further disadvantaged by the use of mean efficacy, which represented a ceiling, despite a number of RCTs demonstrating the efficacy of molnupiravir.

343. The appeal panel concluded as follows:

344. The appeal panel recognised that translating treatment effects into estimates of cost-effectiveness and examination of the uncertainty relating to this could have been addressed in several different ways. The appeal panel recognised that there may have been weaknesses in the approach that was adopted in this evaluation.

345. The appraisal committee and the EAG justified this approach because of significant parameter and structural uncertainty. The justification for the adoption of this modelling approach is described in detail in the EAG reports.

346. Whilst alternative approaches could have been used, the appeal panel concluded that this approach could not be considered to be unreasonable in light of the evidence submitted to NICE and rejected the appeal on this point.

Gilead appeal point 2.1: The Committee's conclusion that significant uncertainty remains in terms of generalisability of the trial evidence for remdesivir in severe COVID-19 is unreasonable because it ignores clinical practice and in-vitro data that has not been countered.

347. Mirko Von Hein, for Gilead, said that in paragraph 3.12 of the FDG the committee stated that most trials pre-dated Omicron and consequently they highlighted four main generalisability concerns: changes in population immunity, changes in pathogenicity, improved effectiveness of supportive care, and other changes specific to the

setting. He stated that the committee concluded that SOLIDARITY was an early study, and no clinical evidence was available for remdesivir in the context of Omicron, the current endemic setting, and the highly vaccinated population. He stated that Gilead consider these four concerns about generalisability are unreasonable stating that,

a. The natural immunity or vaccination status ignores clinical practice. If a patient is hospitalised with severe COVID-19 treatment is required and efficacy unaffected by vaccination status. Vaccination has lowered hospitalisation rates, but once in hospital, some patients are still dying of COVID-19.

b. The committee ignored in vitro data and RWE evidence submitted by Gilead following the second committee meeting. All this evidence shows remdesivir retains potency against Omicron and other variants. He said he would appreciate the opportunity to present other data that substantiates this claim.

c. The committee has not provided adequate reasons as to why different standards of care give rise to generalisability concerns, in particular it has not explained what it considers the differences in standards of care to be between the UK and other countries in SOLIDARITY, and why these differences affect generalisability.

d. The other concerns flagged by NICE were never specified and therefore it is not clear what they are. Gilead therefore believe they are invalid.

He concluded that Gilead think it is unreasonable for the committee to conclude that SOLIDARITY is not generalisable and there should be a third committee meeting to consider SOLIDARITY and allow Gilead to present new supporting data.

348. Professor Stephen O'Brien, for NICE, stated that Gilead are sending out a slightly mixed message about SOLIDARITY. He explained that it

was a very large trial with over 14,000 patients, which showed a small effect of remdesivir, carried out before the emergence of the Omicron variant of COVID-19, and so maybe things have changed. The committee did consider the in vitro evidence, however uncertainty against Omicron remained. He stated that the committee took all the evidence into account; to refute or seriously undermine the generalisability of the trial would have been the wrong thing to do. He stated that they did place quite a lot of weight on it but also took account of other evidence.

349. Dr Richard Nicholas, for NICE stated that the differences between different countries remain. He stated that, for example, Hong Kong is completely different to the UK and vaccination is changing how this disease is evolving. He stated that in the UK hospitalisation has fallen from 14% to 4%. These differences mean that there is a need to focus on data that localises to the UK.

350. Mirko Von Hein argued that it is clear there are changes in immunity, but they do not matter because once you are sick and in hospital, it is no longer a meaningful consideration.

351. Professor Stephen O'Brien stated that this is a reasonable contention, but we do not know if it is true, and it is a difficult point to resolve.

352. Adam Brooke, for NICE, stated that the claim that vaccination status or natural immunity has no effect on efficacy in the hospital setting has no evidence to support it and does not align with what was seen in committee, nor is it aligned with the concept of immune response and how that works. He stated that it is completely plausible that immunity can lessen severity and modify relevant treatment effect, and only a small number of people have seen little change in risk over the pandemic, for example transplant recipients. He cited data from the OpenSAFELY study which he said showed that the general population of hospitalised patients had a greater improvement in outcomes than immunocompromised patients. He stated that,

consequently, the committee did not really accept the argument that vaccination equalises the risk. Finally, the McInnes prophylaxis report documents how people who have suboptimal response to vaccine, even those without antibodies, may develop some kind of immune response.

353. Dr Richard Nicholas stated that people in hospital now are not as unwell as was the case at the beginning of the pandemic. Patients we would now admit would not necessarily have been admitted during the earlier stages of the pandemic.

354. Mirko Von Hein stated that there is data available for overall mortality rates for hospitalised patients, but acknowledged this data was not available during the evaluation.

355. Leena Sathia, for Gilead, stated that the data they had submitted clearly demonstrated that in terms of in vitro activity, remdesivir showed ongoing mortality benefit across different variants of concern. On questioning from the appeal panel chair she did not identify any data that showed retained efficacy of remdesivir as pathogenicity changed.

356. Adam Brooke stated that SOLIDARITY authors talk about heterogeneity, but do not address generalisability to a contemporary UK endemic setting.

357. Stephen O'Brien acknowledged in response to a question from the appeal panel chair that the "other differences specific to pandemic setting," (FDG para 3.12) was vague and accepted that he could not bring any great clarity to the panel about what was meant by that.

358. Adam Brooke stated that he would have hoped the context would be self-evident, and included staff shortages, personal protective equipment (PPE), data collection, fear, less interaction. He agreed that this is a "catch all" that might not be appropriate, however he

stated that he could include examples, which reflect myriad issues that thankfully trouble clinical colleagues less now.

359. Leena Sathia stated that all these things could be addressed at a third committee meeting if Gilead could present new data. Data on mortality was available and would have been picked up in a proper SLR.

360. Adam Brooke in response stated that this data was not in the NMA provided by Gilead.

361. Leena Sathia stated that 70,000 patients in the UK have benefited from use of remdesivir so any concerns about the generalisability of a multinational study because it happened early in the pandemic has been negated by the fact that clinicians are using remdesivir to save lives.

362. The appeal panel concluded as follows:

363. The appeal panel were not presented with any evidence to support Gilead's assertion that differing pathogenicity of COVID-19 variants had no impact on the efficacy of remdesivir. The data on viral neutralisation did not really address questions about changing viral pathogenesis.

364. The appeal panel considered it reasonable that changes in supportive care through the pandemic may have had an impact on the relative efficacy of therapies for COVID-19, and this may affect the generalisability of clinical trial data.

365. The panel considered it reasonable to assume that vaccination status may have some impact on the severity of COVID-19 infection, even in hospitalised patients.

366. The appeal panel concluded that the committee decision was not unreasonable considering the evidence submitted to NICE and this appeal point was rejected.

367. The appeal panel noted that the “other differences” described in the appeal hearing by Adam Brooke should be better defined in a revised FDG.

Conclusion and effect of the appeal panel decision

368. The appeal panel upheld the appeal by Merck Sharp & Dohme on appeal points 1(a)1, 1(a)2, 1(a)3, 1(a)7, and 2.2; Gilead Sciences on appeal points 1(a)1, 1(a)2, 1(a)6, and 1(b)1; and AstraZeneca on appeal points 1(a)1 and 1(a)4.

369. The appeal panel dismissed all other appeal points but would draw the attention of NICE to paragraphs 154, 225 and 367 of this appeal decision that suggest further clarification in the FDG following the panel’s consideration of appeal point 1(a)2 submitted by AZ and appeal point 1(a)3 and 2.1 submitted by Gilead.

370. The evaluation of this technology is remitted to the appraisal committee who must now take all reasonable steps to address the following issues before publishing final guidance. The following paragraphs set out a summary of the principal decisions reached by the panel.

    a. The appraisal committee must address the unfairness resulting from deviation from NICE’s processes for MTA defined in the Manual, specifically, the challenges to stakeholder engagement resulting from the re-sequencing of the appraisal process and the abbreviation of the usual timeframe. The appeal panel cannot dictate to NICE how this should be done. It is the opinion of the panel, however, that it would be difficult to address the very significant concerns identified in this appeal resulting from

the deviation from the usual MTA process without further consultation with stakeholders.

In addition, there are a number of particular issues arising from the panel's conclusions that the panel feel that NICE should address:

b. The panel recognise that there is a rapidly evolving evidence base in respect of this field of medicine; NICE should consider how best to ensure that that all relevant evidence, including Real World Evidence, is identified, evaluated, and critically appraised.

c. The appraisal committee should provide a clear explanation of why the cohort of patients with severe COVID-19 who require low-flow oxygen was not considered suitable for sub-group analysis, and should reconsider whether an analysis of this subgroup would be informative.

d. Stakeholders should be given an opportunity to reflect and comment upon the IVAG report and the conclusions drawn by the committee on the basis of IVAG's work.

e. Paragraph 3.17 of the FDG should be amended to include all relevant therapies. Additionally, the appeal panel invite the committee to revisit the FDG to provide further explanation as to why they did not perform a PSA in the context of paragraphs 4.7.12, 4.7.13 and 6.3.3 of the Manual, and to clarify that an ICER was not disclosed as it was not considered to be informative (paragraph 225).

f. The appraisal committee should reconsider whether their decision not to recommend any therapy for children with severe COVID-19 is a proportionate means to achieve NICE’s legitimate aims.

371. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE’s decision to issue the

final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.