NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]:

Decision of the panel

Introduction

1. An appeal panel was convened on 11 October 2024 to consider an appeal against NICE's final draft guidance, to the NHS, on ruxolitinib for treating non-segmental vitiligo in people 12 years and over.

2. The appeal panel consisted of:

    - Dr Biba Stanton, Chair
    - Jackie Fielding, Non-Executive Director of NICE
    - Mr Christopher Rao, Health service representative
    - David Tyas, Industry representative
    - Sheba Joseph, Lay representative.

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered appeals submitted by Incyte Biosciences UK Ltd ("Incyte" or "the Company"), the Vitiligo Society, Vitiligo Support UK, and the British Association of Dermatologists.

5. Incyte was represented by:

- Pete Williams, General Manager UK & Ireland
- Andy Poll, Head of Value, Access & Pricing
- Amit Mathew, Medical Director, Inflammation & Autoimmunity
- Jaclyn Loh, Senior Manager, HTA Strategy Lead, Inflammation & Autoimmunity.
- Adela Williams, Legal Counsel

6. The Vitiligo Society was represented by:

- Abigail Hurrell, Charity Director
- Catherine Davidson, Trustee
- Alex Schneider, Trustee

7. Vitiligo Support UK was represented by:

- Emma Rush, Chief Executive
- Pav Korpal, Patient expert
- Dr John Ferguson, Lead clinician
- Dr Anthony Bewley, Consultant Dermatologist

8. The British Association of Dermatologists was represented by:

- Professor Viktoria Eleftheriadou, Consultant Dermatologist

- Dr Luba Novakovic, Consultant Dermatologist

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

    - Dr Megan John, Chair of Technology Appraisal Committee D, NICE
    - Professor David Meads, Member of Technology Appraisal Committee D, NICE
    - Dr Jacoline Bouvy, Programme Director, NICE
    - Janet Robertson, Associate Director, NICE
    - Adam Brooke, Health Technology Assessment Adviser, NICE

10. The appeal panel's legal adviser, Amy Smith (DAC Beachcroft LLP), 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. Mark Chakravarty, NICE Lead non-executive director for appeals, in preliminary correspondence had confirmed that:

- Incyte had potentially valid grounds of appeal as follows: Grounds 1(a) and 2.
- Vitiligo Society had potentially valid grounds of appeal as follows: Ground 1(a).
- Vitiligo Support UK had potentially valid grounds of appeal as follows: Ground 2.
- BAD had potentially valid grounds of appeal as follows: Ground 1(a).

14. The appraisal that is the subject of the current appeal provided advice to the NHS on ruxolitinib for treating non-segmental vitiligo in people 12 years and over. 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.

15. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Abigail Hurrell on behalf of the Vitiligo Society, Pete Williams on behalf of Incyte, Professor Viktoria Eleftheriadou on behalf of the British Association of Dermatologists, Emma Rush on behalf of Vitiligo Support UK and Dr Megan John on behalf of the appraisal committee.

Appeal by Incyte

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

Incyte appeal point 1a.1: NICE's refusal to include technical engagement in the appraisal despite requests, by Incyte, was procedurally unfair.

16. Adela Williams stated Incyte's position that NICE's refusal to conduct technical engagement was procedurally unfair and resulted in the negative recommendation of ruxolitinib for treating non-segmental vitiligo. Referring to paragraph 5.7.2 of NICE's current Manual (the Manual), she set out the reasons why Incyte believed that technical engagement would have been "*appropriate, helpful and proportionate – taking into account whether it would resolve key issues before committee meeting*". She stated that - while a matter for NICE - its discretion to hold technical engagement must be exercised fairly in accordance with the factors listed in the Manual. She stated technical engagement was likely needed more where NICE has less experience, that Incyte has identified only two previous NICE appraisals of a topical treatment, that NICE had not appraised a topical treatment in approximately 15 years, and that ruxolitinib was the first specific treatment for vitiligo to be appraised. She stated the External Assessment Group (EAG) appears to have limited experience of the condition. She considered the number of issues that remained outstanding after Appraisal Committee Meeting 1 (ACM1) and after the final draft guidance (FDG) demonstrated that technical engagement was appropriate, and that issues could have been addressed before the first committee meeting. She added that NICE refused technical engagement on the basis that issues were raised in clarification and considered that, as the EAG and Incyte disagreed, it was appropriate to proceed to committee. She stated that this does not address the issue and is procedurally unfair.

17. Dr Megan John, for NICE, explained that NICE appraises technologies of all types and of all types of administration with the same rigour and methods set out in the NICE methods guide. She noted that NICE is adept at appraising a range of different and novel technologies. She explained the chair relies on the NICE Associate Director's expertise regarding whether technical engagement is needed, and that in this appraisal there was an expert much experienced Associate Director who made decision. She stated it is clear from the Manual that technical engagement is NICE's decision alone.

18. Adela Williams stated that this being a topical treatment made a fundamental difference because it introduced inherent uncertainty in dosing, compared to oral or parenteral treatment.

19. Janet Robertson, for NICE, stated that mandatory technical engagement was introduced into NICE's methods in the hope to get to final guidance quicker in more appraisals but that in 2022 the Manual made it optional. She stated that going to technical engagement postpones ACM1 so NICE goes to technical engagement if it expects this will enable the committee to issue positive guidance after ACM1. Otherwise, consultation allows the company and experts to submit whatever may have been said in technical engagement but with the benefit of the committee's view from ACM1. In this case the issues raised by the EAG were too big to resolve at technical engagement, such as comparators and suitability of model structure.

20. Adela Williams stated that whether only one committee meeting would be needed and delay to the process are not reasons given in the Manual for holding or not holding technical engagement, so she argued that this was not a proper basis for decision-making, which should be based on the stated test of whether issues were likely to be resolved before (not at) ACM1. Asked whether those two considerations might not inform the test in the Manual of whether technical engagement was

proportionate and appropriate, Adela Williams accepted that they may do. She stated that Incyte believed issues of positioning, utilities and equalities could have been resolved before ACM1.

21. Jaclyn Loh, for Incyte, stated that the appraisal may have benefited from early dialogue and expert input at technical engagement prior to ACM1 on dosing, the feasibility of an indirect treatment comparison (ITC), the model structure and utility capping.

22. Janet Robertson explained that although both technical engagement and committee meetings are opportunities to engage with experts, the appraisal committee is in a better position to ask questions of experts at a committee meeting rather than the NICE technical team at technical engagement. She stated that the key word in respect of technical engagement is "resolving" issues: it might have been possible to come to ACM1 with more information through technical engagement, but the consultation allows for that too.

23. Dr Megan John stated that given the issues raised by Incyte under this appeal point were not resolved by consultation, it was unlikely that these could have been resolved by technical engagement.

24. Dr Jacoline Bouvy, for NICE, stated that the modelling of the treatment as a mean daily dose was not uncommon in technology appraisal and the approach to dosing did not change between ACMs, so this was unlikely to warrant technical engagement. As to the ITC, she stated that the EAG and Incyte both considered it not feasible and again – as technical engagement focuses on resolving disagreement on key issues – that did not strike NICE as something where it would have been useful. NICE considered that the issues with Incyte's submission identified by the EAG were substantial regarding modelling and uncertainty and that committee views from ACM with a longer time to

address those in consultation would be more helpful and appropriate than technical engagement.

25. The appeal panel concluded as follows. According to the Manual, there is no obligation for NICE to undertake technical engagement. Section 5.7.2 states, “Technical engagement will only be included if NICE considers that it is appropriate, helpful and proportionate, taking into account whether the technical engagement process is likely to resolve key issues before the committee meeting.” Section 5.7.7 states, “The purpose of the technical engagement is to note and consider any evidence gaps and potential resolution ahead of the committee meeting and to consider any commercial or managed access proposals.” Section 5.7.8 further states, “Technical engagement is not a mandatory stage of the evaluation process. When it is identified that the evaluation would benefit from additional engagement before the committee meeting, NICE may decide that the technical engagement process step should be included.”

26. The appeal panel was satisfied that NICE had applied the correct test as set out int the Manual.

27. The appeal panel did not consider the paucity of previous technology appraisals relating to topical therapies or vitiligo was in itself sufficient justification to undertake technical engagement.

28. The appeal panel did not find in Incyte’s evidence during the hearing or the appeal papers evidence of an important aspect of the technology appraisal in which a key issue was likely to have been resolved by technical engagement. In fact, the panel agreed that the key issues at this stage of the appraisal were ones that required committee discussion.

29. The panel therefore identified no procedural unfairness in NICE's decision not to undertake technical engagement.

30. The appeal panel therefore dismissed the appeal on this point.

Incyte appeal point 1a.2: A third meeting of the Appraisal committee should have been scheduled in view of the issues which were unresolved at the second meeting and in order adequately to consider data requested by the committee and submitted by Incyte in response to the draft guidance.

31. Jaclyn Loh, for Incyte, stated that the decision not to constitute a third committee meeting (ACM3) was unfair in circumstances where this was a complex appraisal of a novel treatment, with unclear pathways in a heterogeneous patient population with a complex condition not previously appraised by NICE, compounded by NICE not having appraised a topical therapy for over 15 years. Further, it was unfair that Incyte was deprived of an opportunity to respond to the EAG's critique of its evidence and changes to the FDG after the second committee meeting (ACM2).

32. Dr Megan John, for NICE, stated that there would always be new issues to consider at further meetings, but NICE is tasked with making decisions and cannot avoid doing so by obtaining comments on every change. She stated that the company has an opportunity to comment on the EAG report and draft guidance, and it does not have a right to comment on everything. She stated that there is an opportunity cost of an ACM3 for the relevant patient population and for others and the NHS as a whole. She further stated that there were two weeks to read the papers before ACM2 and that ACM2 is scheduled to be shorter than ACM1 and the committee reject the idea that the second meeting was shorter than usual in this appraisal. She noted there was not a large number of questions in part 1 of ACM2 as the main outstanding

issues were around utility values and modelling outputs and Incyte chose to mark those as confidential, and the committee discussion is in part 2 of the meeting.

33. Janet Robertson, for NICE, stated that NICE was satisfied after ACM2 that all issues raised in consultation had been discussed, so it disagreed with Incyte's view that an ACM3 was required due to inadequate time on the issues. She said NICE routinely considers a further consultation but if the committee accepts what the company has submitted at the first consultation, then a further consultation is pointless. In this case, new evidence (a revised model) was presented by Incyte, and the committee accepted that model (albeit acknowledging its flaws) and did not consider further consultation would improve the model. Nor were there any changes of mind that NICE considered needed consultation.

34. Andrew Poll, for Incyte, when asked what required consultation, stated that the issues of comparators, age, dosing and a revised economic model, coupled with what felt like a rushed ACM2, warranted an ACM3.

35. Jaclyn Loh stated that because NICE had accepted Incyte's revised model without further consultation and despite considering it flawed, this resulted in a more conservative view of the incremental cost-effectiveness ratio (ICER) overall. Further, Incyte believed that the decision making on capping utility values was the single factor for non-recommendation, and that this was not raised in draft guidance, so Incyte had no opportunity to provide additional data. Therefore, this required further consultation after publication of final draft guidance.

36. Adela Williams, for Incyte, stated that the process point was that the EAG had made criticisms of Incyte's new evidence that amounted to substantial significant evidence and that the committee seemingly

accepted, and Incyte did not have an opportunity for consultation in relation to those criticisms. That is why Incyte say ACM3 was needed.

37. Adam Brooke, for NICE, stated that in respect of utilities, the committee changed its position in the FDG but considered this well justified and explored in the earlier stages of the appraisal. On the model, he referred to 3.10 of the FDG explaining that the model was accepted, albeit the committee acknowledged its biases. He accepted that ACM3 would have guaranteed more discussion but not that fairness required this. The purpose of ACM3 would be to accommodate a second consultation but Incyte had not suggested what new evidence it would have presented, and the committee already had the evidence it required to make a judgement.

38. Professor Viktoria Eleftheriadou, for the British Association of Dermatologists, suggested that some of the uncertainties may have been resolved through greater engagement with clinical and patient experts in committee meetings.

39. Dr Megan John explained that the committee had considered the clinical and patient input in detail on the papers ahead of the committee meeting, which negated the need for prolonged questioning at the committee meeting itself.

40. Professor David Meads, for NICE, explained that the utility values were capped on the basis that the initial utility values were higher than those of the general population and that capping was therefore standard practice. He explained that there was an issue with non-responders having a dip in health-related quality of life (HRQoL) (and subsequently utility value) compared with the average population and on reanalysis this dip had been even greater, which was a big driver of value in the appraisal. These things brought into question the validity of the utility data, and that the EAG scenarios around this introduced huge

uncertainty in the plausible ICERs. He stated that it was the non-responder utility value, not the capping, which had a big impact on the ICER.

41. Dr Jacoline Bouvy, for NICE, explained that the committee had real doubts about the extent to which the economic model presented by Incyte appropriately reflected the condition, health state and response (or non-response) experienced by patients using ruxolitinib and therefore considered there to be structural uncertainty. She explained when the model is not suitable for decision making, it is difficult for a committee to arrive at a strong view on its elements, such as utility capping, hence that decision was taken at FDG stage. She reiterated the view that capping of utilities so that they are not higher than the general population is common and that therefore it would not have been proportionate to consult or convene a further committee meeting to consider this. NICE considered the draft guidance signalled this issue and the FDG was more of an iteration than significant change.

42. Adam Brooke, when asked by the panel why the range of ICERs in the FDG differed from the range of ICERs in the EAG exploratory analysis, explained that this was a function of the model. The committee had considered a range of scenarios, with and without capped utility values. The lowest ICER in the FDG was requested after the second committee meeting based on the committee's conclusions and was subsequently validated by the EAG.

43. The appeal panel concluded as follows.

44. The appeal panel understood that a third committee meeting is not mandated by the Manual and is unusual. However, a third committee meeting may be needed if there is a significant change in the interpretation of the data, or introduction of data between the first and second appraisal committee meeting that result in a significant change

in the recommendation warranting further consultation. Specifically, section 5.8.59 of the Manual states, “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.”

45. The panel therefore considered whether a third ACM was required in the particular circumstances of this case as a matter of procedural fairness. The panel did not agree with Incyte’s view that stakeholders must have the opportunity to be consulted on every piece of evidence or decision in an appraisal. The panel therefore considered whether the specific issues raised by Incyte in the appeal required consultation as a matter of fairness. Incyte suggested that the EAG critique of the ITC, resulting in the appraisal committee’s decision not to use the ITC to inform the ICER, represented a significant change. The panel considered evidence from the EAG report, and evidence from the hearing, that the EAG had been consistent in their approach to an ITC between ruxolitinib and phototherapy throughout the appraisal process. The panel understood that the committee’s position was that the ITC had value in informing the positioning of ruxolitinib but was not useful in informing the ICER directly. The panel did not think that this amounted to a significant change in the appraisal committee’s position following the first appraisal committee meeting that would require further consultation.

46. The appeal panel considered the appraisal committee's approach to utility capping to be a standard approach and also did not represent a significant change in the committee approach.

47. Finally, the panel were unable to identify any significant change in the approach of the appraisal committee between the first and second

appraisal committee meeting in either the appeal documents or hearing. Consequently, the appeal panel considered the various issues raised and the difference in preferred committee base-case ICER to Incyte and EAG ICER to be a consequence of incremental decision making rather than a significant change in approach by the appraisal committee.

48. Overall, the panel judged that NICE had carefully considered whether a third ACM was needed, with reference to the process set out in the Manual, and that it was appropriate for NICE to bear in mind the opportunity cost of a third ACM (in terms of NICE resources that would be diverted away from other technologies). The panel agreed that a third appraisal committee meeting was not necessary as a matter of procedural fairness in the particular circumstances of this appraisal.

49. The appeal panel therefore, dismissed this appeal point.

Incyte appeal point 1a.3: The committee's conclusion that the indirect treatment comparison of ruxolitinib cream and phototherapy was not robust due to variation in baseline characteristics between studies is unexplained.

50. Incyte's Appeal Point 1a.3 and the British Association of Dermatologists' Appeal Point 1a.1 were discussed together. That discussion is reported below.

51. Jaclyn Loh, introducing Incyte's Appeal Point 1a.3, stated that while the EAG and the committee had commended Incyte for its ITC of ruxolitinib cream and phototherapy, the results were dismissed. She said the committee's conclusion was unexplained, as it was based on alleged differences between in baseline characteristics between the patients in the HI-Light and TRuE-V trials but it was unclear which characteristics

were deemed problematic and there was no opportunity to clarify or address these concerns to ensure the ITC was considered.

52. Professor Viktoria Eleftheriadou, introducing the British Association of Dermatologists' Appeal Point 1a.1, stated that the explanation given in sections 3.4 and 3.6 of the FDG rejects the ITC on the basis the EAG thought it unreliable but gave no other reasons. In particular the FDG did not adequately explain why the differences in baseline characteristics were a cause for concern. She noted that the main differences between the trials were age and duration of treatment. She stated different baseline characteristics are not an unusual feature, and that the failure to give an adequate explanation meant that there was no opportunity to comment on whether the differences were prognostically or otherwise important. She stated that an adequate explanation would have enabled clinicians to assess how generalisable the study results are to their patient population and adapt accordingly. She stated that the results from the TRuE-V trials were similar to the patient profile in secondary care, and that it was unclear from the FDG whether this was considered in relation to the difference in baseline characteristics.

53. Professor David Meads, for NICE, stated that the ITC was not critical to the committee's final decision making. Both the EAG and Incyte had agreed that the ITC would not be valid, and that there are concerns broader than the baseline characteristic variation. He said it is key in an ITC that the primary endpoints are the same – and that this was not the case for the HI-Light and TRuE-V trials. This was in the EAG's public report if not in the FDG. Although the committee concluded that the ITC was not valid for generating ICERs, the committee found it useful in providing a steer about the relative benefits of using phototherapy and ruxolitinib, which supported the clinical experts' qualitative evidence

that ruxolitinib is substantially more effective. This helped justify the positioning of ruxolitinib in the clinical pathway before phototherapy.

54. Jaclyn Loh explained that despite Incyte initially choosing not to put forward an ITC as it would not be robust, the committee told it to present an ITC following ACM1 as key to decision making. She explained that Incyte had sought an extension of time to produce and provide this analysis.

55. Andrew Poll, for Incyte, stated that ACM2 gave no real opportunity for discussion of the ITC, or the issues raised. He stated that the appraisal did not reach the point of knowing if this model was useful.

56. Dr Megan John, for NICE, stated that companies attend ACMs to answer specific questions from the committee and that ACMs are not opportunities for companies to give greater explanation: that opportunity is in the paper the company submits to committee, which committee digests at length, and in the consultation process. The issues with an ITC were in the draft guidance and the EAG view had been aired. There is not an opportunity for the company to respond to every comment, including the EAG's comments, as that would extend the appraisal process indefinitely and harm patients and the wider NHS population. The committee relies on companies to present all information and answer questions in the consultation periods available.

57. Adam Brooke, for NICE, stated that it was clear from the first committee meeting that the value of any ITC analysis would be confirmatory as a comparison against phototherapy. He stated that the context of paragraph 3.6 was that Incyte originally said in the feasibility assessment that an ITC would not be appropriate, and the EAG report (para 3.4.2) explained the EAG had no confidence in the ITC results due to concerns regarding baseline characteristic variation between the two studies, including as to disease status and mean T-BSA (% of the

total body involved). There was back and forth between Incyte and EAG before ACM2. Paragraph 3.6 of the FDG explains the EAG's position and, at the end of the paragraph, states the committee's conclusion that the analysis justified the clinical opinion that ruxolitinib cream would be used before phototherapy because of the increased clinical efficacy, but did not provide a robust enough comparison to inform cost utility analyses.

58. Adam Brooke, when asked by the panel whether the intention of seeking an ITC was to confirm the positioning rather than influencing an ICER, explained that the analysis would always be limited given the trial design and that the committee did not expect to receive analysis robust enough to inform an ICER when it had sought the ITC from Incyte.

59. Adela Williams, for Incyte, noted that as NICE had sought the analysis after the first committee meeting, it was incumbent on NICE to provide adequate reasons for rejecting the analysis provided. She stated that paragraph 3.6 does refer to various EAG concerns but does not explain them or the basis of committee's decision.

60. Jaclyn Loh stated that Incyte wanted to know if there were any other reasons the committee did not use the ITC to inform cost utility analyses beyond the limitations of which NICE was aware before it requested the ITC.

61. Adam Brooke stated that the feasibility of the ITC had been considered in the EAG report, so Incyte had a considerable amount of time to respond, or to engage in discussion on the strengths and weaknesses of the analysis in their response to consultation.

62. Dr Megan John stated that paragraph 3.6 makes clear that the committee had asked for further ITC analysis, which was considered by

the committee but was not considered robust enough to inform cost utility analysis.

63. Dr Jacoline Bouvy, for NICE, added that it is very difficult for a committee to take a view on how robust analysis will be until and unless it is presented with the analysis.

64. The appeal panel considered Incyte's Appeal Point 1a.3 and the British Association of Dermatologist's Appeal Point 1a.1 together in their discussion. The appeal panel concluded as follows.

65. The appeal panel were satisfied that section 3.6 of the FDG made the committee's approach to decision making regarding the ITC very clear, and indeed were rather surprised that it could have caused any confusion. The FDG states "The committee considered that the analysis justified the clinical opinion that ruxolitinib cream would be used before phototherapy because of the increased clinical efficacy, but did not provide a robust enough comparison to inform cost utility analyses." This sentence directly follows on from a discussion of the EAG critique of the ITC, so it is evident to a reader that this critique informed the committee's conclusion that the ITC was not robust enough to use in cost-utility analysis. The panel were also aware that the level of detail required in the FDG depends on the relevance of a particular issue to the final decision. In this case, the fact that the ITC was not used to inform cost-utility analysis was **not** a key driver of the decision, so the panel did not think that more detailed explanation was required.

66. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness on this issue and dismissed both Incyte's appeal point 1a.3 and BAD's appeal point 1a.1.

Incyte appeal point 1a.4: The committee has failed to give an adequate explanation of how it has complied with the Equality Act 2010.

67. Adela Williams, for Incyte, stated that the committee's conclusion that there were no equality issues relevant to the recommendations (paragraph 3.20 of the FDG) was unexplained and appeared to conflict with the available data. She stated that as a public body, NICE is subject to the provisions of the Equality Act 2010 (EqA 2010) and must therefore take protected characteristics, several of which were relevant to this appraisal, into account in its decision making. She stated that the focus of Incyte's appeal point was race. She referred to NICE's Public Sector Equality Duty (PSED) pursuant to section 149 of the EqA 2010 to "have due regard" to the need to advance equality of opportunity between persons who share a relevant protected characteristic and persons who do not share it, which involves:

> "having due regard, in particular, to the need to:
>
> (a) remove or minimise disadvantages suffered by persons who share a relevant protected characteristic that are connected to that characteristic;
>
> (b) take steps to meet the needs of persons who share a relevant protected characteristic that are different from the needs of persons who do not share it; and
>
> (c) encourage persons who share a relevant protected characteristic to participate in public life or in any other activity in which participation by such persons is disproportionately low."

68. Adela Williams stated that Incyte had outlined in its appeal letter the data and consultation responses which evidenced the greater disease burden experienced by vitiligo patients with darker skin tones. She stated that the committee noted various impacts at 3.20 of the FDG but

then concluded simply there were no equalities impacts raised by appraisal without justifying that conclusion in the context of the overwhelming conflicting evidence to the contrary. She stated that the committee ought to have explained in its conclusion at paragraph 3.20 of the FDG how it considered the different needs of vitiligo patients from protected racial backgrounds. She stated the Committee referenced that impact varies between individuals not necessarily linked to skin tone, and that Incyte understand this came from the response to the committee's question during the appraisal of whether people with lighter skin tones experience adverse impact. She stated that no further exploration was permitted of this issue and that the fact that individuals with lighter skin tones may require treatment does not mean this appraisal raises no equality issues. She concluded her introduction of this appeal point stating that NICE had, in Incyte's view, failed to meet the PSED and failed to give any reasons or explanation of why it rejected the evidence made available to the committee of a disproportionate impact of vitiligo on people with darker skin tones.

69. Dr Megan John, for NICE, stated that the committee had been acutely aware of equality issues related to vitiligo in its appraisal of ruxolitinib. She described the evidence heard and considered by the committee on the matter – including the social context, the increased stigma that vitiligo patients with darker skin tones experience and the associated psychosocial element. Nonetheless, the committee had also been presented with evidence (in particular, from the patient support groups) that the psychosocial impact of vitiligo is highly variable from individual to individual, and that greater psychosocial impact does not always correlate to darker skin tone or a protected characteristic. She explained that the committee did not want to make a recommendation which would restrict access to ruxolitinib to only patients with a particular skin tone. Discussing the evidence, she said that Incyte's modelling did not consider any difference in HRQoL between different

skin tones, nor did it consider any psychological costs separated by Fitzpatrick scores. The committee lacked evidence on differences of quality of life or efficacy. Further, she stated that, as the FDG is a document that is used in NHS clinical practice, it must be usable and understandable which means a detailed explanation cannot be provided for every conclusion. She suggested the explanation the Company was seeking may be in the accompanying papers.

70. Adela Williams disagreed and stated that it is fundamentally important for the committee to provide adequate reasoning to justify its conclusion given the importance of the EqA 2010.

71. Adam Brooke, for NICE, stated that it is not within NICE's remit to eliminate discrimination but rather to consider if a recommendation could cause discrimination. He stated that where there is a negative recommendation, i.e. where a treatment is not recommended for anyone, this cannot be discriminatory as there is no inequality of opportunity. [The panel in its deliberation on this point understood this statement to mean that a negative recommendation cannot raise equalities issues in terms of prioritising access for one group over another, given the treatment is not recommended at all, but it noted that all recommendations (negative and positive) require consideration under the EqA 2010].

72. Adam Brooke stated that the committee do go through what is required by the EqA 2010 but if they had to explain this in detail in the FDG this would be cumbersome and legalistic and was not required by 6.1.9 of the Manual. He referred to 6.2.9 of the Manual regarding whether a subgroup was appropriate and to 6.1.9 of the Manual regarding the language and style used in the FDG. He apologised to patient groups that it was not clear from the way FDGs are written that equalities issues do not typically modify a committee's recommendation but inform whether subgroup choices are appropriate. He stated that the

committee considered the patients in the clinical trial were generalisable to UK patients so the data in the trial should capture impact accurately.

73. Adela Williams, when asked if she agreed that the committee had considered the evidence but reached its conclusion on the basis that there was no quantitative evidence to support disproportionate impact, stated that the PSED required NICE to request the evidence itself, rather than expect stakeholders to provide it. She reiterated that it was incumbent on NICE to consider the evidence regarding greater impact on those with darker skin tones and to explain how it had done so in the FDG. She stated Incyte did not make a case for a subgroup recommendation and that particular needs could be considered in a range of ways; Incyte's appeal point is that the FDG does not explain if and how the committee did that.

74. Dr Megan John, when asked whether the committee agree that there is no conflict in the evidence showing both a disproportionate impact for those with darker skin tones and that people with lighter skin tones may also experience significant impact of vitiligo, stated that the committee were cognisant of that but that the committee was not able to make an optimised recommendation as that evidence had not been presented to the committee. When asked whether there were other options open to the committee, other than making an optimised recommendation, she stated that one option is to adapt the ICER threshold – however this was not an option in the appraisal for ruxolitinib as the evidence to enable that was not provided. She repeated the suggestion that a negative recommendation does not discriminate in terms of access. She added that the committee had gone further than what was required to consider possible inequalities by requesting a second patient expert.

75. Dr Jacoline Bouvy, for NICE, said that the committee had understood that people with protected characteristics were not more likely to

develop vitiligo but that the impacts of vitiligo were felt more severely in people with darker skin tones.

76. Dr Anthony Bewley, for Vitiligo Support UK, disagreed, stating that for those with darker skin tones there was a greater disease incidence and more significant psychosocial comorbidities.

77. Adela Williams, when asked by the panel whether the Equality Impact Assessment published alongside the FDG provided adequate reasoning for the decision, expressed the view that the only document that can be subject to appeal is the FDG, though other documents may be considered if specifically referenced.

78. Dr Megan John noted that the committee acknowledged that there were equality issues, but that it was not possible to address those issues through its decision making, and that was what was meant by the conclusion in the FDG. She stated that the committee understood vitiligo has a greater impact on people with darker skin, but there was no evidence on the impact of treatment with ruxolitinib on QoL being greater for those people: it is possible to accept the disease impact is greater but there was no evidence this treatment would address or mitigate that. She stated she did not think the committee could have reached a different conclusion but accepted it could better support patient organisations in particular to understand the way NICE writes its decisions in FDGs and to make it clearer that what the committee meant by its conclusion at 3.20 FDG was that the committee could not address the recognised equalities issues in its decision.

79. Jaclyn Loh, for Incyte, stated that Incyte had submitted evidence for a subgroup of patients with Fitzpatrick skin scores of 4-6, and had demonstrated that ruxolitinib was more cost effective in that subgroup. However, the EAG had dismissed this analysis on the basis that the clinical end point is not more impactful for those in the subgroup.

80. Adela Williams concluded discussion of this appeal point by reminding the panel that this was a Ground 1a appeal, focusing on transparency, and that there was no indication in the FDG of whether and how the committee took into account the differential impact of vitiligo on people with darker skins. She suggested that if the committee's reasoning is not in the FDG then "it didn't happen". She also challenged the committee comment that a negative FDG could not be discriminatory.

81. The appeal panel concluded as follows. It first noted this appeal point was brought by Incyte under ground 1(a) (procedural unfairness) and not ground 1(b) (NICE has exceeded its powers). It referred to the scrutiny correspondence in this regard: it noted Incyte had expressly decided not to bring a point that NICE had breached the EqA10 (by failing to discharge its PSED or otherwise) and instead the point referred to the panel was whether the committee had provided an adequate explanation of how it had taken into account the equalities issues listed at paragraph 3.20 of the FDG and reached the conclusion that there were no equality issues relevant to the recommendations.

82. In considering this appeal point the panel did not agree with the view taken by Incyte that the only document that can be appealed is the FDG. It noted section 7.1 of the Manual states "consultees can appeal the final draft guidance, or the process followed using the appeal process."

83. Nor did the panel agree with Incyte's submission that if any aspect of the appraisal process is not specifically mentioned in the FDG then "it did not happen". Rather, it considered the hearing an opportunity to explore the committee's evidence on what had happened.

84. As this appeal point related to transparency the panel accepted that the key document was the FDG but considered all the publicly available

documents relating to the appraisal process, including the equality impact assessment.

85. The panel discussed what it understood the committee's position to be. The appeal panel accepted NICE's evidence in the hearing that the committee were conscious that people with darker skin may be disproportionately affected by vitiligo, but did not feel that there was any mechanism available to the committee within NICE's process and methods to address this. The panel accepted that this was what was meant by the statement in the FDG that "there were no equality issues relevant to the recommendations".

86. Turning to the key issue of transparency, the panel did not consider paragraph 3.20 of FDG provided sufficient explanation of the appraisal committee's reasoning, even when considered together with the equalities impact assessment. In particular, the concluding statement that “there were no equality issues relevant to this appraisal” did not follow logically from the rest of the paragraph. Although at the hearing it became clear that the committee had *intended* this to mean that there was no mechanism available to the committee within NICE's process and methods to address the equality issues that had been identified, this would not be clear to a typical reader of the FDG. The panel noted that there was general agreement on the importance of equality issues in this appraisal (with respect to both age and race), and therefore judged that it was necessary as a matter of fairness for the FDG to give a detailed and logical explanation of the committee’s reasoning on this point. The panel agreed with the argument that patients, clinicians and decision makers would be unable to understand why the appraisal committee did not consider there to be any relevant equalities issues.

87. The appeal panel concluded, therefore, that there was procedural unfairness here and upheld the appeal point.

Appeal by the British Association of Dermatologists

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

British Association of Dermatologists appeal point 1a.1: The committee acknowledges that ruxolitinib cream is more effective than phototherapy, but then ignores the indirect treatment comparison (ITC), not even relying on it as providing a direction of travel for its conclusions. This is an unfair application of NICE's procedures.

88. There was substantial overlap between this point and Incyte's appeal point 1a.3, and the panel considered these points together. The panel concluded as set out in paragraphs 64-66 of this decision letter.

89. The appeal panel therefore dismissed the appeal on this point.

Appeal by the Vitiligo Society

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

90. The Vitiligo Society's appeal points 1a.1, 1a.2 and 1a.3 were introduced together in the appeal hearing. The introduction is reported together below, and the discussion is reported separately below.

91. Abigail Hurrell, for the Vitiligo Society, stated by way of introduction that the Vitiligo Society's points 1a.1, 1a.2 and 1a.3 cumulatively show unfairness. She stated that the Vitiligo Society is uniquely placed to advocate on behalf of underrepresented voices in the vitiligo patient population. She stated that the burden of vitiligo for young people is higher than for adults and that it is difficult for young people to access treatment, as phototherapy is often disruptive to education. Further, she explained that the Vitiligo Society work to redress systemic health inequalities faced by vitiligo patients with darker skin tones and that the

systemic health inequalities experienced by this group were not adequately represented or understood in this appraisal, including that those with darker skin tones are also more likely to represent lower socioeconomic groups, and are less likely to be able to travel for appointments, participate in clinical trials and/or have work patterns which make accessing treatments inaccessible. Emphasising the importance of patient engagement and consultation in the appraisal process, she stated that NICE ought to provide patient support groups with adequate support, setting clear expectations of the participation required, the scope of work and services provided, and should give adequate time to respond. She requested that NICE provide more time for engagement and hold an ACM3.

Vitiligo Society appeal point 1a.1: NICE failed to act fairly by declining all expert nominations from the Vitiligo Society and therefore excluding representation from the committee meetings.

92. Addressing Vitiligo Society's appeal point 1a.1, Dr Megan John, for NICE, expressed gratitude to the patient experts who attended ACM1 and stated that they did an excellent job. She explained the chair is responsible for selecting patient and clinical experts applying criteria under the Manual. In particular, NICE selects experts on the basis of their experience of the technology and condition and experts ideally have complementary rather than similar experience. She stated that she had inherited the appraisal for ruxolitinib from another committee chair, and at that time two clinical experts and a patient expert (from Vitiligo Support) had already been selected. The Manual provides that, usually, a maximum of two patient and two clinical experts are selected for each evaluation. She was cognisant of the potential equalities impact of this appraisal and therefore asked NICE to seek nominations for a further patient expert. NICE received nominations from the Vitiligo Society and Vitiligo Support UK. Dr John explained that having

considered both nominations, the committee selected Vitiligo Support UK's nominee because she wanted someone with lived experience of having darker skin and of navigating having a protected characteristic in relation to which the committee had heard there is increased burden. She stated that the experts are not selected on the basis of the nominating organisation as expert are asked to represent their own experience (not the group's). Where NICE does not select a nomination from a society that is not NICE suggesting that the society is not representative, but a function of being able to accommodate limited number of people at the meeting and the wealth of information the committee receives overall. She added that committees consider all evidence with parity of esteem – whether advanced in a scoping workshop, as written feedback, or public comments on the draft guidance document or by experts in the meeting. She stated that a committee could never hope to capture the full range of impact from four experts in a committee meeting, which are an opportunity for the committee to ask questions in response to written submissions. She stated that other patient groups were invited to provide written submissions, and these are helpful as they can be longer, and the committee has time to digest them.

93. Abigail Hurrell, for the Vitiligo Society, when asked by the panel what additional or different expertise the Vitiligo Society nominee would have offered if selected, stated that it was impossible to say what would have happened if its patient expert were in the room.

94. Megan John, when asked whether the committee had identified any gaps in patient expertise that was not available to it in the committee meeting, confirmed it had not. She stated that the two patient experts selected were a trustee for Vitiligo Support and a patient living with vitiligo. The former was a strong advocate for the wider community and the latter was able to share a first-hand account of his lived experience

of the disease. ACM1 is where the committee ask probing questions to form the draft guidance and its questions were thoroughly answered by patient experts there. The committee also took the unusual step of asking the clinical experts if they wanted to raise issues, given that they treat many patients, and the committee wanted to ask as many sources as possible.

95. Dr Megan John, when asked by the panel whether the clinical or patient expertise present at the meeting represented young people, explained that the committee asked the experts to give a broader view of the wider community that they represented. She stated that age is not on the nomination form and the nominee of Vitiligo Society was good but did not emphasise they would offer insight from younger people or bring a particular thing. She reiterated that it is impossible to capture the entirety of experience within a patient group through two patient experts alone.

96. Professor Viktoria Eleftheriadou, for the British Association of Dermatologists, suggested that parents of children with vitiligo may have been appropriate patient experts. Referring to Janet Robertson's explanation earlier in the discussion, that more than two clinical experts may be needed in an appraisal where multiple disciplines are involved in treatment, she suggested that as treating vitiligo and its impacts often requires input from psychiatrists, as well as dermatologists, it may have been appropriate to consider exceeding the usual maximum of two clinical experts. Janet Robertson, for NICE, noted that had a stakeholder suggested another clinical expert from another discipline, the committee would have considered the request.

97. The appeal panel concluded as follows.

98. The appeal panel acknowledged the lengths to which the Chair of the appraisal committee went to ensure that there were experts selected

who had lived experience of the personal and social difficulties of living with vitiligo. The panel was aware that there is no obligation in NICE processes to select a patient expert nominated by every consultee, and that chairs have discretion in the selection of experts. In this case, the panel agreed that the chair had clear and strong reasons for selecting as the second patient expert someone with darker skin colour (rather than the expert nominated by the Vitiligo Society).

99. The appeal panel noted that appellants were satisfied with the evidence given by the selected experts during the appraisal committee meetings. The appellant did not persuade the panel that the selection of patient experts led to any important gaps in the evidence available to the committee. In addition, the panel noted that there are multiple opportunities for patient experts to contribute to the appraisal process, and that committees give equal weight to written submissions as to evidence they hear at committee meetings.

100. Overall, the appeal panel were satisfied that the Chair of the appraisal committee complied with NICE's process and methods in selecting experts and that the approach taken had not prevented the Vitiligo Society from making a full contribution to the appraisal process.

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

Vitiligo Society appeal point 1a.2: NICE failed to act fairly by giving notice of only 3 days to make a written response to the Phase 1 scoping consultation.

102. Turning to the Vitiligo Society's appeal point 1a.2, Abigail Hurrell, for the Vitiligo Society, explained that, as a result of an administrative error, the Vitiligo Society received the consultation documents on the scope of the appraisal with only three days to provide a response. The

documents were sent to an incorrect email address in error. The error was identified when NICE's patient participation team followed up with the Vitiligo Society on 18 April 2023 to see whether it was intending to provide a written response to the consultation. Once the Vitiligo Society confirmed that it had not yet received the scoping consultation documents, NICE provided the documents and asked if the Vitiligo Society would be able to provide comments by 21 April 2023.

103. Janet Robertson, for NICE, explained that the NICE patient support team had supported the Vitiligo Society throughout the process, that the Vitiligo Society could have asked for more time and that NICE would likely have accommodated any such request. She stated that the Vitiligo Society also sent representatives to the scoping workshop. She stated that the Society had sufficient opportunity to raise any serious concerns about the scope and she could not see how they were disadvantaged, or how the scope might have been different.

104. Abigail Hurrell, when asked by the panel what the Vitiligo Society would have done differently had they been given more time to respond to the consultation documents, explained that the Vitiligo Society would have been able to reach out to certain underrepresented communities within the vitiligo patient group. She also explained that the Vitiligo Society did not ask for further time to provide a response as this would have delayed the appraisal process and, given the other patient experts and support groups participated in the process, the Vitiligo Society expected that patient voices would have been comprehensively represented. While the other voices were excellent at representing their communities, ultimately the Vitiligo Society felt the impact of ruxolitinib was not captured fully in the process.

105. Abigail Hurrell, when asked by the panel why the Vitiligo Society could not have addressed any outstanding issues at the scoping workshop (which took pace four weeks after the scoping consultation), stated that

there was insufficient time to consult with the patient population it represented ahead of the scoping workshop.

106. The appeal panel concluded as follows. Section 2.5.3 of the manual sets out the process for consultation on the draft scope as follows: "Consultations are either 28 days (long), 14 days (medium), or 7 days (short). Long consultations will be used if there is a reasonable degree of uncertainty about elements of the draft scope or whether the technology should be evaluated. If the draft scope contains only a small degree of uncertainty, or a scope has previously been well defined in other related NICE outputs in the last 12 months, a medium or short consultation may be used." In this case, NICE had decided that a 28-day scope was appropriate. There was common consensus in the appeal hearing that NICE had made an error by sending the consultation documents late to the Vitiligo Society.

107. The appeal panel did not consider an error in sending papers late to an appellant would always represent procedural unfairness, particularly if efforts are made by NICE to mitigate any unfairness introduced by deviations from its usual process.

108. The appeal panel were sympathetic to the appellant's argument that this had more impact for a small charity with no experience of NICE appraisals, compared with other consultees, because the truncated consultation period afforded them only three days to comment on the scope in writing and there was not much time for them to understand the technology appraisal process, which can be difficult given the technical language and concepts inherent in the technology appraisal process. The panel was aware that the Vitiligo Society is a small charity that had not had prior experience of the NICE appraisal process, and that there was felt to be a reasonable degree of uncertainty about elements of the draft scope. However, the panel were also aware that the issues at scoping are often more accessible to stakeholders and

less technical than questions about economic modelling arising later in the appraisal process.

109. The appeal panel did not expect the appellant to provide a detailed assessment of how the appraisal process would have changed if the Vitiligo Society had had more time to understand the process, engage with the community that they represent and prepare a written response, but it did expect the appellant to identify possible impacts. The appeal panel noted the assertion by the appellant that the Vitiligo Society had expertise in engaging with young people and that they did not have sufficient time to engage with the wider vitiligo community, including younger patients. The panel accepted that the truncated consultation period reduced the overall time available to the appellant to understand NICE's scoping process and engage with patients.

110. However, the appeal panel also noted that NICE had made efforts to support the Vitiligo Society at the start of the process, such as offering an induction meeting (which the appellant had not taken advantage of) and providing an induction pack, which helped explain NICE's process. It also noted that representatives of the appellant attended the scoping workshop, which was held four weeks after the scoping consultation and which afforded a further opportunity for the appellant to consult with patients and comment on the scope. Further, it noted that the appellant had understood that it could ask for further time to provide a response but decided not to do so because this would have delayed the appraisal process.

111. Finally, whilst the panel were surprised that the particular impact of vitiligo on young people had not been given more weight during the appraisal and FDG (see Vitiligo Support UK's appeal point 2.1 below) it considered that there were several opportunities for this issue to be raised during scoping and at later stages of the process, and that in the committee documents it is apparent that the committee were indeed

aware of the disproportionate impact of vitiligo on children and young people.

112. Overall, the panel determined that NICE did deviate from its process but considered that whether this amounted to procedural unfairness was very finely balanced in this case and, taking into account all of the circumstances described above, concluded that it did not.

113. The appeal panel therefore dismissed the appeal point.

Vitiligo Society appeal point 1a.3: NICE failed to act fairly by giving notice of only 13 days to make a Phase 2 written submission.

114. Janet Robertson, for NICE, explained that as a result of an email being sent to the Vitiligo Society's participants at the scoping workshop instead of its named contact, the Vitiligo Society only had 13 days (instead of the usual 56 days) to respond to make a written evidence submission.

115. Abigail Hurrell, for the Vitiligo Society, explained that the repeated errors (highlighted in both its appeal points 1a.2 and 1a.3) made it difficult for the Vitiligo Society to engage with the appraisal process.

116. Dr Jacoline Bouvy, for NICE, stated that NICE and specifically the people and communities involvement team at NICE tries its very best to ensure organisations who engage with NICE's processes are supported throughout. She stated they had offered an induction meeting at the start of the process and the Vitiligo Society had declined this. She explained that the patient participation team had regular communication with more than one contact at the Vitiligo Society, and that this had contributed towards the confusion.

117. Adam Brooke, for NICE, explained to the panel that all stakeholders receive an induction pack at the beginning of the appraisal process

which specifies what is expected at each stage. He added that concerns about underrepresentation of younger people were not raised in the consultation responses throughout the appraisal.

118. The appeal panel concluded as follows.

119. Section 5.5.10 of the manual sets out the process for the company to submit written evidence to NICE: It states that the deadline for receipt of written evidence is 56 days from the invitation to participate in single technology evaluations. Section 5.5.32 of the manual states that non-company stakeholders should be given the same number of days and deadline.

120. There was agreement in the appeal hearing that NICE had made an error by sending the invitation to participate late to the correct Vitiligo Society contact so that they had only 13 days to make a written submission.

121. The panel once again considered the key issues discussed in its finding on Vitiligo Society appeal point 1a.2: that deviations in process do not necessarily mean there is unfairness, that truncated periods to prepare written submissions may have a greater impact on small charities who are not experienced in NICE processes, and that it would expect the appellant to highlight what impact this issue had on the appraisal process.

122. As to potential impact, the panel were aware of the Vitiligo Society's particular expertise in supporting young people and that it would have liked more time to reach out to this patient community to inform written submission of evidence. Again, the panel considered that the appellant understood it could have sought an extension to facilitate this and did not do so. Further, it was evident that the committee were aware of the impact of vitiligo on children and young people from paragraph 3.1 and

3.30 of the FDG. However, the panel considered that the disproportionate impact of vitiligo and its treatment on children and young people could arguably have been more fully considered (see Vitiligo Society UK's appeal point 2.1 below). Given the importance that NICE places on written submission of evidence, which was emphasised in the hearing by the Appraisal Committee Chair, the panel accepted that the appellant might have been disadvantaged by a truncated period to prepare a written submission. In particular, the shorter time to reach out to the community that they represent and serve before preparing the written submission to NICE may have meant that an opportunity to highlight the importance of the disproportionate impact of vitiligo on children and young people was missed.

123. In contrast to appeal point 1a.2 by the Vitiligo Society (in which there was opportunity to raise issues at the scoping workshop) there was no equivalent opportunity in this situation as appraisal committee meetings are not an opportunity for stakeholders to make additional arguments or present new evidence, and the importance of written submission of evidence in the NICE appraisal process is well recognised. Further, the panel noted the requirement to provide written evidence on the clinical effectiveness and value for money of the technology, reflecting the experience of patients, impact of the technology on health-related quality-of-life, and feasibility of implementation of the technology. The panel considered this to be a substantially more time consuming and technical document (more so than the scope) for a small charity with limited experience of the NICE process to produce. The panel therefore considered that the appellant might have been particularly disadvantaged by the shorter period for preparation of written submissions.

124. Overall, the panel determined that NICE did deviate from its process but (again) considered that whether this amounted to procedural unfairness was very finely balanced in this case. Taking into account all of the circumstances described above, the panel agreed that the Vitiligo Society had been disadvantaged in the preparation of written evidence, that this may have had an effect on the appraisal process, and that this amounted to procedural unfairness.

125. The appeal panel therefore upheld the appeal point.

Appeal by Incyte

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

Incyte appeal point 2.1: The committee has disregarded real world evidence and expert evidence for the purposes of decision-making on dosing.

126. Jaclyn Loh explained Incyte's view that the committee's decision to prefer the most conservative estimate was without justification and unreasonable. This disregarded real world evidence that the use of ruxolitinib cream was much lower than the dosage evidence in clinical trials, which significantly inflated the ICER.

127. Dr Megan John, for NICE, stated the committee did consider all the evidence including real world evidence on dosing but it was difficult to calculate because no clinical evidence was presented about how it would be reduced in real world.

128. Professor David Meads, for NICE, stated that dosing is very complex in this evaluation, because of the nature of administration and the evidence to support. He explained that the economic model was based around data from the TruE-V trials. He stated modelling cannot capture the real-world nuance of administering a treatment as there are multiple

different ways of dispensing and applying the treatment that may affect dosage and only one value can be put into the model. He explained that the doses in the trial are baked into that value, and that it would not be appropriate to uncritically accept change to just one parameter of value in the model based on real world evidence. He explained that, if the committee were to accept reduced dosage estimates influenced by real world evidence, it would expect to also see relative reductions in clinical effectiveness as the dosage was lowered, and it did not see that. Although the committee were happy to consider real world evidence, it was not appropriate to use this to change the model where it was the only parameter of value to be changed within the model.

129. Adam Brooke, for NICE, explained that Incyte did not argue that the dosing estimate from the real-world data should be used in the model. The choice was between EAG's base case (using the mean dose from the trial) and Incyte's base case (used a log-transformed mean from the trial). Incyte did not provide data on the statistical goodness of fit for this. He accepted there are likely to be differences between the model and use in clinical practice and stated this is a common issue. In this appraisal Incyte gave the trial evidence and made a case for that. It provided limited explanation of the real-world evidence and how the committee could grapple with that information, and there were reasons to think the US database real world data may be substantially different from expected use in UK clinical practice. The committee would have valued seeing real world evidence to demonstrate how people responded differently but this would not allow it to separate out how the treatment will be used.

130. Jaclyn Loh responded by explaining that the log-normal mean was used by Incyte as the base case as they acknowledged the limitation with real world evidence, but nonetheless Incyte considered the real-world evidence useful as the committee and EAG could contextualise

the ruxolitinib usage. She noted that there is other evidence showing that the dosage in the trial studies are approximately 2-4 times more than that used in real life. She stated Incyte would have provided additional analysis if it had been requested. Although she acknowledged that this did not have a significant impact on the ICER, she stated a lot of the uncertainty was not in favour of the product.

131. The appeal panel concluded as follows. It understood Incyte's argument that real-world dosing might be lower than that seen in the TruE-V trial because the trial population had a higher mean body surface area affected than the real-world population. It noted that Incyte had not asked for the dose based on its real-world evidence to be used in its model, but instead had argued that this evidence provided context to support using the log-transformed mean value from the trial data (which was lower than the mean preferred by the EAG).

132. The panel judged that the committee had considered all the evidence before it, including the real-world data. They had been aware of the limitations of this real-world data and the substantial uncertainty about the most likely dose in UK clinical practice. The committee had agreed with Incyte that the real-world estimate of dosing should not be used in the model when other key aspects of the model were derived from the trial data. They had considered the option of the log-transformed value from the trial but were concerned that Incyte had not provided data on its statistical fit.

133. The appeal panel concluded that several approaches could reasonably be taken to modelling dosing in this appraisal. However, the panel was confident that the committee had considered all the evidence, weighed the pros and cons of different approaches, and reached its conclusion in a logical way. The panel therefore judged that the committee's approach had been reasonable.

134. The appeal panel therefore dismissed the appeal on this point.

Appeal by Vitiligo Support UK

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

Vitiligo Support UK appeal point 2.1: The appellant contends that the treatment of health inequalities in the FDG was unreasonable in that, first, it did not reflect the discussion that took place, which would reasonably be expected to have been reflected in the FDG.

135. Emma Rush, for Vitiligo Support UK, stated that equality is a key issue, and that Vitiligo Support UK wanted both in the ACM and now to emphasise that vitiligo can have a significant psychosocial impact across all skin types. She stated that the rationale at paragraph 3.20 of the FDG did not adequately reflect the discussion that took place in the committee meeting: although vitiligo is a condition that can have significant impact across all Fitzpatrick skin scores, the FDG did not provide a reasonable account of the impact of stigmatisation on those with black or brown skin tones. She stated that a reasonable person would consider this group to experience more stigma and associated trauma, and that the committee ought to have taken that into account. Further, she stated that age was not reasonably considered by the committee. She described the impact of vitiligo on young people – having an impact on formative years of education, friendships, intimate relationships and embarking on a career. She explained that the current phototherapy treatment pathway was disruptive to schooling, exams, attendance at university and in the workplace. She stated that it was unreasonable that this protected characteristic was not considered and/or not mentioned in the FDG.

136. Pav Korpal, for Vitiligo Support UK, gave a moving account of his lived experience of vitiligo. He described how he had experienced bullying from a young age and that he faced cultural stigma.

137. Dr John Ferguson, for Vitiligo Support UK, echoed Pav Korpal's words, and described his experience of holding a vitiligo clinic in London. He described that approximately 70-80% of his patients in the vitiligo clinic had darker skin tones, which was not reflective of the general population in the clinic's surrounding area. Dr Ferguson also noted that, in his experience, the impact was often greater on teenagers and women. He also supported the real-world evidence that patients would often use far less ruxolitinib cream than was stated as the dosage in the TRuE-V trial. He challenged the notion that a negative recommendation cannot be discriminatory.

138. Dr Anthony Bewley, for Vitiligo Support UK, also provided insight from his clinical practice. He agreed that vitiligo affects people with darker skin more commonly and stated that the committee were right that psychosocial comorbidities do not correlate with disease extent. He emphasised the severe burden of living with vitiligo and stated that while there may not be evidence of ruxolitinib providing benefit, it was known that if the skin improves then so will the psychosocial burden.

139. Dr Megan John, for NICE, recognised the severe impact of vitiligo. She confirmed the committee accepted all of the points regarding disproportionate impact related to age, race, and sex and that these were raised in scoping workshop, the ACM1 papers and at the ACM1. However the committee has to make decisions on the basis of the evidence, and Incyte had not submitted evidence to show that ruxolitinib has a differential impact.

140. Adam Brooke, for NICE, referred to section 3.1 of the FDG which described the greater impact of vitiligo on various groups, including

young people and that 3.17 of the FDG recognises different quality of life considerations for newly diagnosed individuals. He stated the main issue the committee had was operationalising this information in meaningful way. He added that the patient population in the TRuE-V trial was broadly representative of the UK population, and that it was therefore generalisable in terms of ethnicity makeup of the trial. There was no evidence to support the committee making an optimised subgroup recommendation based on skin type, which was what the committee were considering in the equalities section of the FDG.

141. Adam Brooke reiterated that submissions from both the British Association of Dermatologists and Vitiligo Support UK at the committee meetings had emphasised the fact that vitiligo can be psychologically devastating irrespective of skin tone. The committee had understood, as a result, that neither Incyte nor the patient support groups were seeking an optimised recommendation. Incyte did not provide evidence to support subgroups.

142. Emma Rush agreed it was never Vitiligo Support UK's preference to advocate that treatment be limited to one patient group only. She explained that, from a patient support group view, optimisation narrows the benefit – which is sub-optimal for a group which seeks to support and represent the entire patient population.

143. Professor Viktoria Eleftheriadou, for the British Association of Dermatologists, referred to NICE's appraisal of baricitinib for treating severe alopecia areata and suggested that referral criteria for treatment with ruxolitinib in secondary care could be based on psychological impact. Emma Rush agreed.

144. Jaclyn Loh, for Incyte, stated that the EAG had dismissed Incyte's subgroup analysis on the basis that there was no difference in effectiveness between those with lighter and darker skin tones.

145. Dr John Ferguson stated that it was self-evident that psychological benefit from effective treatment will be greater for patients with darker skin.

146. Dr Jacoline Bouvy, for NICE, explained that a difference in HRQoL was not evidenced in the quantitative trial data from Incyte.

147. Dr Megan John acknowledged the frustration around this issue. She explained that even if something is obvious in clinical setting, NICE still needs the company to present this to it in a way the committee can operationalise in the model, as NICE has to see clinical and cost effectiveness analyses to make a recommendation.

148. Adela Williams, for Incyte, stated that the committee is required to take account of the expert evidence as well as the company's evidence. She stated there was limited discussion of health inequalities in the committee meetings so Incyte was not aware of the information it now heard the committee would have liked to see regarding benefit of the treatment for people with darker skin tones.

149. Dr Jacoline Bouvy stated that the committee had taken all the evidence it had heard on this topic into consideration in its decision making, and had sought to report that discussion accurately in the FDG. She noted that although stakeholders may disagree with the conclusion, that does not necessarily make it an unreasonable conclusion to have reached on the basis of the evidence considered by the committee.

150. The appeal panel concluded as follows.

151. The panel discussed the committee's approach to considering the impact of vitiligo on people with brown and black skin tones. At the hearing, it was clear that the committee understood that although vitiligo can have an important psychological impact on people of *any* skin tone, it does have a disproportionate impact on people of colour

(especially in terms of stigma and cultural impact). However, the panel were concerned that section 3.20 of the FDG did **not** make it clear that the committee accepted that vitiligo has a disproportionate impact on people with brown and black skin tones, or how this had informed its decision-making. In particular, the final sentence of section 3.20 stating that "there were no equality issues relevant to the recommendations" simply did not make sense, so the panel judged this to be unreasonable.

152. In addition, the panel were concerned that the committee had not given sufficient consideration to the potential for vitiligo to have a disproportionate impact on young people. This is briefly alluded to in section 3.1 of the FDG but not mentioned at all in the equalities section of the FDG (3.20; this section mentions that vitiligo is more common in young people but not that it may have a greater impact) or in the equalities impact assessment. The panel were aware that the committee can only consider the evidence before it. However, the disproportionate impact of vitiligo on children and young people is mentioned in the consultation documents. The panel concluded that this issue should have been given greater weight and more detailed consideration by the committee, and it was unreasonable not to do so.

153. The appeal panel therefore upheld the appeal on this point.

Conclusion and effect of the appeal panel's decision

154. The appeal panel upheld the appeal by Incyte on appeal point 1(a)4; the Vitiligo Society on appeal point 1a.3; and Vitiligo Support UK on appeal point 2.1.

155. The evaluation of this technology is remitted to the appraisal committee who must now take all reasonable steps to address the issues raised in the upheld appeal points before publishing final guidance.

156. 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.