NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Single Technology Appraisal of degarelix for treating advanced hormone-dependent prostate cancer [ID590]

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 25th June 2014 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on Single Technology Appraisal of degarelix for treating advanced hormone-dependent prostate cancer.

2. The Appeal Panel consisted of –

   Mr Paddy Storrie – Appeal Panel Chair
   Prof. Finbarr Martin – Non-Executive Director
   Dr Ashutosh Wechalekar – NHS Representative
   Dr Mark Chakravarty – Industry Representative
   Mr Bob Osborne – Lay representative

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The Panel considered appeals submitted by Ferring Pharmaceuticals, Tackle Prostate Cancer, and the British Uro-Oncology Group.

5. Ferring Pharmaceuticals was represented by –

   Mr Gavin Gandy - Divisional Manager, Ferring Pharmaceuticals
   Dr Anne Bro Falkenberg - Global Medical Affairs, Ferring Pharmaceuticals
   Mr Grant Castle - Legal Counsel Covington and Burling LLP
   Mr Nic Brereton - Health Economist, Ferring Pharmaceuticals
   Dr Patrick Davey – Cardiologist

6. Tackle Prostate Cancer was represented by Mr Hugh Gunn, who was also able to offer the perspective of a patient with this condition.

7. The British Uro-Oncology Group was not present at the appeal hearing, and their appeal letter was taken into account.

8. All the above declared no conflicts of interest.

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

   Prof. Gary McVeigh – Chair, Technology Appraisal Committee D
   Dr Lindsay Smith - Vice-Chair, Technology Appraisal Committee D
   Mr Meindert Boysen - Programme Director, NICE
   Ms Helen Knight - Associate Director, NICE

10. All the above declared no conflicts of interest.

11. The Institute's legal adviser Mr. Stephen Hocking (DAC Beachcroft LLP) was also present.

12. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

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

    Ground 1(a) NICE has failed to act fairly
    Ground 1(b) NICE has exceeded its powers
    Ground 2 the recommendation is unreasonable in the light of the evidence submitted to NICE

14. The Vice Chair (Dr Maggie Helliwell) in preliminary correspondence had confirmed that appellants had potentially valid grounds of appeal as follows: Grounds 1(a) and 2.

15. Degarelix is a selective gonadotrophin-releasing hormone (GNRH) antagonist that reduces the release of gonadotrophins by the pituitary, which in turn decreases the secretion of testosterone. GNRH suppression is used as a method of treating hormone dependent prostate cancer and can be done with both GNRH agonists and antagonists. Because GNRH antagonists do not produce an initial increase in testosterone levels (testosterone surge), which may occur with GNRH agonists, there is no risk of symptomatic tumour flare with this agent. Degarelix has a UK marketing authorisation for "treatment of adult male patients with advanced hormone-dependent prostate cancer". It is administered as a subcutaneous injection.

16. The appraisal that is the subject of the current appeal provided advice to the NHS on degarelix for treating advanced hormone-dependent prostate cancer.

17. Before the Appeal Panel inquired into the detailed complaints, the following made a preliminary statement: Mr G Castle on behalf of Ferring Pharmaceuticals, Mr H Gunn on behalf of Tackle Prostate Cancer and Prof. G McVeigh on behalf of the Appraisal Committee.

Appeal by Ferring Pharmaceuticals and Tackle Prostate Cancer and the British Uro-Oncology Group

Appeal Ground 1: NICE has failed to act fairly

Ferring Pharmaceuticals - Appeal Point 1.1a: ***NICE failed to issue a second ACD following a substantial change to the preliminary recommendations that significantly reduces the number of eligible patients that can be treated with degarelix***

and

Tackle Prostate Cancer – Appeal Point 1.1a: ***the wording of the proposed guidance has changed significantly between ACD and FAD without re-consultation***

and

British Uro-Oncology Group – Appeal Point 1.1a: ***Change in wording from ACD to FAD without consultation***

18. *With the agreement of all parties present these appeal points were considered together*

19. Mr Castle, for Ferring Pharmaceuticals, stated that there was substantial change in the wording for patients in whom Degarelix is recommended between the ACD and FAD. The wording in the ACD stated use was recommended for patients who are "at risk of impending spinal cord compression". This was changed to wording in the FAD which states that treatment was recommended in patients who "present with signs or symptoms of spinal cord compression". Mr Castle said this change in wording of recommendations has three significant consequences: **a.** restricting and reducing the patient group eligible to receive the drug by 85%. The patients eligible to receive Degarelix decreases from approximately 3520 per annum to 520 due to the changed recommendations, **b**. The change in the recommendation of Degarelix from ACD to FAD from impending to actual spinal cord compression repositions the treatment from a precautionary measure to, at best, an ameliorative one and **c.** essentially restricts the use of this agent to patients who have advanced disease without much prospect of any benefit from treatment (so are at a therapeutic "dead-end").

20. Dr Davey, for Ferring Pharmaceuticals, said that spinal cord compression is a devastating complication of the illness. By the time patients are presented with spinal cord compression, the disease consequences were much different to an earlier disease stage. They may have a momentum which is impossible to arrest. A substantial proportion of patients may not make it to the oncologists for definitive therapy and spinal cord compression can be an end of life event in an elderly patient. Radiotherapy and/or surgery, which are the standard options for treating this complication, are not possible in a significant proportion of frail elderly patients.

21. Mr Castle, for Ferring Pharmaceuticals, further said that the recommendation was changed without allowing Ferring the right to review and answer or to produce new/additional evidence. Hence, Ferring felt that due to substantial change in recommendations, a second ACD would be fair and allow appropriate consideration of any additional evidence.

22. Mr Gunn, on behalf of Tackle Prostate Cancer, said that spinal cord compression is a horrifying prospect for a patient - everything should be done to prevent this from occurring. Once signs and symptoms had occurred, it was too late. He had mentioned in his opening statement that he felt the change in wording mentioned above is a small change in terminology, but a huge change for the patients concerned. It was unclear why or on what evidence this change was made and the process lacked transparency.

23. Prof. McVeigh, on behalf of the Appraisal Committee, said the fact that there was the change in the wording did not mean a change in the patients the Committee intended to receive treatment. The intention was always to treat only patients with impending or actual spinal cord compression. The Appraisal Committee has indeed considered the devastating effects of spinal cord compression. He said that patients with “impending” or “actual” spinal cord compression are a subgroup referred to in the scope. The manufacturer had submitted no cost effectiveness evidence for that subgroup as none existed. ERG exploratory analysis of cost effectiveness by subgroup had no evidence basis and it was unclear if there would be a difference in cost effectiveness for the “at risk of impending or actual spinal cord compression” subgroups. ERG made assumptions to explore a possible additional benefit for some patients, including assumption that Degarelix would prevent all spinal cord compression. Prof. McVeigh said his was a generous assumption as Degarelix was not a treatment for spinal cord compression. It recognized the advantage provided by Degarelix - that it does not produce a testosterone flare, consequences of which may or may not include spinal cord compression.

24. Prof McVeigh said the Committee had had to "swallow hard" to accept additional benefit for this patient subgroup as evidence in this setting was essentially non-existent. Some of the assumptions accepted for modelling purposes were known to be wrong (for example, that Degarelix prevents *all* spinal cord compression). The Committee was not recommending Degarelix as a treatment for spinal cord compression, which was a subject of NICE guideline CG75.

25. He mentioned that “impending” meant an event about to happen and in case of spinal cord compression this would be predicted by new symptoms of cord or root compression as described in NICE clinical guideline 75. Without these symptoms a clinician could not know that compression was impending. He was very clear that it was not the intention of the Committee to change the meaning of the guidance in any way between the ACD and FAD. He also addressed the point raised by Ferring about restriction to a smaller patient population. As far as the Committee was concerned, it was always the same group of patients eligible in the FAD and ACD. It was always the intention of the Appraisal Committee in both the ACD and FAD that Degarelix was indicated for patients who were “about

to develop or had developed" spinal cord compression. The intention of the Committee in the FAD was to be specific and accurate in the guidance issued. All the Appraisal Committee had done was to "tighten" up the recommendation to aid NHS clinicians in the interpretation of the guidance.

26. Dr Lindsay Smith, on behalf of the Appraisal Committee, said that CG75 lists signs and symptoms of spinal metastasis not just spinal cord compression. He pointed to the relevant sections in CG75.

27. Prof. McVeigh, on behalf the Appraisal Committee, added that he was unclear where the reduction in patient number originated (85% or 75% as mentioned by Ferring in their statement). Spinal metastases are common in prostate cancer but spinal cord compression is uncommon. He added that the Committee tried to clarify this but there was a lack of data. A patient/physician can only know that spinal cord compression is "impending", which means "about to happen" when a patient develops signs and/or symptoms. He also mentioned that the high risk patients group with PSA >20 was a completely different patient group. He accepted that the wording in the ACD should have been more precise. However, it was his understanding that Ferring had understood the Committees' meaning of the wording in ACD.

28. Dr Lindsay Smith, from the Appraisal Committee, pointed to section 4.21 in the ACD where the manufacturer did not include a model for this subgroup. It was assuming no spinal cord compression in patients on Degarelix and spinal cord compression occurring only in patients on agonists at modelled rates of 5%, 10% and 50%. The clinical experts said that the Degarelix would not prevent all spinal cord compression. Hence, the Committee was persuaded by the ERG analysis which suggested that if the rate of spinal cord compression exceeded 3.5% Degarelix was dominant.

29. Prof. McVeigh again added that to be "impending or at risk" a patient had to exhibit signs and symptoms. He added that the Committee re-worded to clarify what the Committee meant by "at risk of impending".

30. Mr Castle, on behalf of Ferring, responded to this clarification by stating that the effect of what he described as a change in focus was now to restrict Degarelix to an acute emergency setting and focus on a different patient group. He pointed out that CG75 differentiates between at risk of spinal cord compression and those with signs and symptoms of spinal cord compression. The change in FAD reduced the target patient population by 85% (he said that according to NICE it was a reduction by 75%). The meaning of the words "at risk of impending" and "with signs and symptoms of" were very different.

31. Dr Davies, on behalf of Ferring, added signs and symptoms of spinal cord compression are not always as classical as mentioned by the Appraisal Committee leading to difficulties and delay in diagnosis/identification of this complication until a late stage; especially as a number of those symptoms are already common in an elderly population.

32. Mr Paddy Storrie, Chair of the Appeal Panel, clarified from both the Committee (Prof. McVeigh) and Ferring (Mr. Gandy) their understanding of the wording as it changed through the ACD to the FAD. Prof. McVeigh reiterated that the Committee always meant that “at risk of impending” and “with signs and symptoms of” as one and the same all the way through the process and had not intended any changes. Mr Gandy, for Ferring, said that the company’s understanding was that a very different patient group was implied by the ACD wording, as against that ultimately adopted.

33. The Appeal Panel applied the test set out in the Institute's process guide for STAs paragraph 3.5.35. This reads:

    [where there has been] *a substantial revision of the ACD, involving a major change in the recommendations, considerations and/or evidence base, the Centre Director and the Chair of the Appraisal Committee will decide whether it is necessary to prepare another ACD.*

34. This is a two stage test. First, the Panel must decide if there has been a substantial revision/major change. If no, no question of a second ACD arises. If yes, the Panel must consider whether it was unfair for the Centre Director and Chair of the Appraisal Committee not to have prepared a second ACD.

35. The first question is a matter for the Panel's judgment having regard to the objective meaning of all of the material in and supporting an ACD and a FAD. The intended meaning of the Committee in either document is irrelevant save to the extent that it can be demonstrated from the documents produced. The purpose of an ACD is to inform consultees of likely guidance and the reasons for it. They cannot be expected to know what is in the mind of the Committee, unless it is evident in the ACD or a supporting document. The purpose of a FAD is to offer guidance to the NHS reader. Again, they cannot be expected to know the mind of the Committee.

36. The Panel concluded without hesitation that the change in wording between ACD and FAD was a substantial revision leading to a major change. Mr Castle was correct to say that the change was from precautionary use to something else. While there was some doubt over the exact numbers he was also very likely to be correct to say that the patient population who would benefit under the wording used in the FAD would be much smaller than the population who would have benefitted under the wording used in the ACD. On both grounds this was objectively a major change.

37. The Panel moved on to consider whether it was fair not to have issued a second ACD. This is a question for the Panel's own judgment. The Panel concluded it was unfair not to have prepared a second ACD. The Panel understands that it is in the nature of a consultation that the proposal consulted on might change. The Panel was aware that such a change does not as a matter of law require a reconsultation unless it is "fundamental". The Panel considers that the Institute has set itself a somewhat more stringent test than this in the language of paragraph 3.5.35, but still affirms that there may be major changes that do not require a second consultation.

38. However in this case the change was truly fundamental. The Panel felt that the wording in the ACD describing patients “at risk of impending spinal cord compression” objectively meant that the event had not actually happened in the patients, but there was a more than fanciful possibility of this event happening. On the other hand, a wording in the FAD referring to patients who present with “signs and symptoms of spinal cord compression” meant that the risk had actually crystalized. There was no longer a prospective risk. Spinal cord compression was taking place and generating symptoms.

39. Furthermore, the reason for the change in wording was not anything said or any new evidence submitted by a consultee, but the Institute realising that its original wording did not accurately capture the decision of the Committee. That very realisation must call into question whether consultation on the original wording can have been fair. The Panel disagreed with Professor McVeigh that Ferring's consultation submissions showed it understood that only patients with actual spinal cord compression were to benefit. The Panel felt that consultees had been misled as to what was being proposed, albeit wholly inadvertently, and through no fault of the Committee. The Panel noted Dr Smith's observation that the result of a reconsultation must necessarily be the same but with respect to him, until the entire Committee has received and considered consultees' comments on this issue, he cannot be sure of this.

40. As a result the Panel was not satisfied that the consultation that took place was fair. The only fair course open to the Committee on these particular facts would have been to prepare a second ACD.

41. The Appeal Panel therefore unanimously upheld this appeal point.

42. Further steps on this issue are for the Committee. The Appeal Panel observes that there is a challenge in this group of patients to accurately identify patients in whom spinal cord compression is a relevant consideration, and for whom treatment with Degarelix is cost effective. There may be a number of different approaches to the problem and different outcomes, and provided these are fairly consulted on and are reasonable, it is not the business of an Appeal Panel to say what they should be. In the hope that it may assist the Committee and consultees, the Panel observes that it felt that the NICE clinical guideline 75 was helpful but not necessarily determinative on this point in this population group. It felt that efforts should be made in any future ACD/FAD to accurately define the patient population if the technology is to be approved for a particular patient group, so that the NHS will be able to effectively operationalise such a decision. The Appeal Panel does not under-estimate the challenge of doing this. The Committee may want to consider whether the better way forward is to consult on the wording now contained in the FAD, or to offer some other wording informed by the discussion at the appeal and unconstrained by past drafting.

Appeal by Ferring Pharmaceuticals

Appeal Ground 1a: NICE has failed to act fairly

Ferring Pharmaceuticals - Appeal Point 1.2(a): ***The decision in the FAD to restrict use of degarelix to patients with spinal metastases who have actual spinal compression (as opposed to those who are "at risk" of spinal compression) lacks transparency and fails to give adequate reasons***

And

Tackle Prostate Cancer - Appeal Point 1.2(a): ***No additional evidence is presented to explain the change of wording from ACD to FAD which lacks transparency***

43. At the outset, Mr Paddy Storrie, Chair of the Appeal Panel on behalf of the Appeal Panel, pointed out the inconsistency in wording in the appeal point submitted by Ferring. The wording used in the FAD is "adults with metastases who present with signs or symptoms of spinal cord compression" and not "patients with metastases who have actual spinal compression" as stated in the appeal point. He also pointed out that overall, in the scope, ACD, FAD and discussion, there was laxity in use of wording to define the defined patient group by all parties including the appellants, the Appraisal Committee as well as the clinical experts.

44. Mr Castle, on behalf of Ferring, said that the current point linked directly with Appeal Point 1.1a. Ferring was not consulted, there was no additional ERG evidence to explain a change in wording and no consultee or commentator had argued or requested that the recommendation in the ACD be narrowed or the wording changed. Prof. McVeigh's comment on the intent of the Committee, which according to Prof. McVeigh was the same in the ACD and FAD, was not reflected in the wordings of the public documents. He pointed to sections 3.33, 4.11 and 4.19 of the ACD, specifically to the points highlighted in the appeal submission from Ferring, all of which discuss the patient group which was at risk of spinal cord compression and not a patient group which had developed signs and symptoms of spinal cord compression. He said the Appraisal Committee had accepted ERG evidence relating to an "at risk of impending spinal cord compression" patient group He was unaware of a discussion with any consultee over the change in wording which took place between ACD and FAD, and failed to understand why the same ERG evidence could point to two apparently different conclusions. He maintained if the wording was to be changed, a second ACD should have been issued otherwise the wording of the original ACD should have been maintained.

45. Prof. McVeigh, from the Appraisal Committee, said the NICE Guidance Executive felt that the guidance lacked "sharpness" and asked for the patient group to be clarified. He felt that this could be and had been done while not varying from the formed intent of the Committee.

46. There was brief discussion about the role of NICE Guidance Executive in the change in wording.

47. Mr Boysen, Programme Director NICE, clarified that NICE Guidance Executive reviews the FAD before final publication to ensure clarity of language in FAD, and may go back to the clinical experts in order to ensure that guidance was clear and may suggest clarification of wording prior to publication. This had happened on a number of occasions in the past.

48. Prof. McVeigh, on behalf the Appraisal Committee, said that the change in wording was to make the FAD more precise. NICE Guidance Executive had consulted the ERG clinical expert and sent the draft FAD back to Prof. McVeigh for clarification in the wording. He had sent it out to clinical experts but received a reply from only one expert.

49. Ms Helen Knight, Associate Director NICE, clarified that the intent of the Guidance Executive had been to clarify the wording as the Guidance Executive felt the previous wording did not accurately delineate the group of patients who would benefit from Degarelix. The Committee spoke to the ERG clinical expert and the suggested change in wording was sent back to the Committee chair, Prof. McVeigh, who agreed with the change. The NICE Guidance Executive was familiar with the intent of the Appraisal Committee and did not feel that this was a "major" change and, hence, there was no requirement to go back to the consultees.

50. Mr Paddy Storrie, Chair of the Appeal Panel, sought clarification from Ferring about their understanding of this part of the process.

51. Mr Castle, on behalf of Ferring, said that if there was no common understanding that the terms used in the ACD and FAD meant the same, the change made would be clearly major and hence it was not a fair process. He further commented that the very clinical experts consulted by NICE over the change in wording, had now appealed the FAD on behalf of British Uro-Oncology Group because of the effect the new wording would be likely to have on the eligible patient group.

52. The Appeal Panel considered the arguments presented and unanimously concluded that there had been a major change in the wording between FAD and ACD. In this case fairness would have required the reason for such a change to be given. Without reasons, consultees were left with the same evidence base justifying two objectively very different recommendations, and that called for explanation. The Panel now understood that the reason was to "clarify" wording and not to actually change the target population, but had that been stated, appellants would have been able to argue that the change in wording made had that latter effect, a view that the Appeal Panel supports.

53. The Appeal Panel, therefore, unanimously, upheld these two appeal points.

Appeal by Ferring Pharmaceuticals

Appeal Ground 1a: NICE has failed to act fairly

Ferring Pharmaceuticals - Appeal Point 1.3(a): ***The FAD recommendation is not sufficiently clear, precise or understandable for the NHS and is therefore not in accordance with the STA Guide or principles of good administration.***

54. Mr Castle, for Ferring, said that the FAD does not give clear guidance. The SPC for Degarelix has an initial dose followed by an ongoing maintenance dose. There is no authorisation in the SPC for "emergency" use. The current recommendation in the FAD effectively positions Degarelix as an emergency treatment, does not explain the emergency use, transition from secondary care to primary care and is unclear about the need for continuing maintenance therapy. This will lead to confusion regarding the use of the agent.

55. Mr Gandy, from Ferring, stated that they had evidence that the drug was being used outside of the SPC and general practitioners were stopping or switching to another therapy. This conclusion was drawn from order data audited by Ferring, vials of Degarelix supplied for starter vs. maintenance pack (1:7 changing to 1:1 respectively) and market research of specialists. The latter showed that 45% of consultants who responded to a survey said that patients had been switched against their wishes. Guidance for continuous therapy needed to be explicitly clarified in the FAD.

56. Mr Castle, from Ferring, further added that the FAD recommendations may be interpreted literally and the SPC may not be consulted or followed after the NICE recommendations.

57. Prof. McVeigh, from the Appraisal Committee, said that he struggled to understand how the guidance could be expected to have such effects. He stated very clearly that the issue of switching was not raised, discussed or presented at any point. The Committee had never discussed use outside of SPC and never recommended “off label” use. Additionally, the issue of use in primary or secondary care was never discussed. The Committee understood that, in most patients, androgen deprivation therapy will continue until death. He also added that which drug of a range of drugs to choose or switching or not between therapies was an issue more appropriate for a clinical guideline and not a technology appraisal.

58. Mr Gandy, from Ferring, said that switching was not an issue at the ACD but had become an issue due to the restrictive recommendations in the FAD. He asked for a clear and tighter recommendation to continue therapy with Degarelix.

59. The Appeal Panel considered these points. The Appeal Panel concluded that the Appraisal Committee had not recommended use outside of the SPC at any time. The guidance itself in the ACD or FAD did not suggest any use outside of the licensed indication, nor did it seem likely to encourage such use. The precision or otherwise of the current recommendation had no bearing on whether switching

was more or less likely to take place. Guidance has to be of manageable length, and Appraisal Committees are entitled to assume its readers will be familiar with the SPC, and will either prescribe in accordance with it or have an appropriate reason for doing otherwise. The Committee would have been in some difficulty in commenting on switching, as it had been offered no evidence on the subject, and an STA was not an appropriate forum to consider issues that would be better considered, if at all, in a guideline. Provided switching was neither recommended nor a foreseen, inevitable and avoidable consequence, and it was not, the Committee could not be criticised.

60. The Appeal Panel, therefore, unanimously dismissed this appeal point.

Appeal by Ferring Pharmaceuticals

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

Ferring Pharmaceuticals - Appeal Point 2.1: ***The assumptions upon which the ERG and Appraisal Committee has based their assessment are unreasonable in light of the evidence of cardiovascular risk submitted.***

And

Ferring Pharmaceuticals - Appeal Point 2.2: ***The failure to recommend degarelix for patients at risk of cardiovascular disease is unreasonable in light of the evidence submitted***

61. *With the agreement of all parties appeal points 2.1 and 2.2 were considered together*

62. Mr Castle, for Ferring, stated that the assumption of the Appraisal Committee in assuming that the cardiovascular risks of GNRH agonists and antagonists are equal is unreasonable in the light of evidence presented.

63. Dr Davey, for Ferring, said that there was increased cardiovascular risk for patients with pre-existing cardiovascular disease when GNRH agonists are used. Use of antagonists markedly reduces this additional risk. Submitted meta-analysis of trials and expert option was overwhelmingly in favor of reduction of cardiovascular risks. He said that the suggestion of the Appraisal Committee to consider a randomized clinical trial to prove this point would be unethical in light of current evidence. There is no animal model that can be studied. He said that the current NICE recommendations would result in over 3000 excess cardiovascular events. He argued that hormone agonists have a different overall impact on cardiovascular complications since androgen deprivation after orchidectomy does not increase cardiovascular risk. This may be due to differential suppression of FSH and LH. He also added that a third of all prostate cancer patients are at risk of cardiovascular events and would benefit from Degarelix with reduction in that risk.

64. Mr Castle, for Ferring, stated that the current evidence does not support the conclusion that cardiovascular event rates were equal with GNRH agonists and antagonists. The ERG should have been instructed to model cardiovascular risk and queried why even exploratory analysis was not undertaken. Specifically, he said that, on appeal point 2.2, if cardiovascular risk had been included, the ICER for Degarelix would have been very different.

65. Prof. McVeigh, on behalf of the Appraisal Committee, said that in a single technology appraisal, it was the manufacturers' responsibility to present appropriate evidence and models. No cardiovascular models were presented. He discussed in details the Albertson *et al* paper of meta-analysis of Degarelix trials. He specifically discussed the studies in the forest plot on page 6. Of the six studies included in the meta-analysis, only three were presented in the paper since there were no cardiovascular events in the other three studies. Of the three studies presented in the forest plot, the entire effect was driven by one small study which showed an 85% reduction in the cardiovascular risk. He pointed out that he was unaware of any drug or technology that lead to such a marked reduction of cardiovascular risk in any patient group and even statins reduced cardiovascular risk by only 20%. The main reason for this apparent yet remarkable risk reduction was the very small number of cardiovascular events in the CS37 trial – only 13 events were recorded (10 in the comparator and 3 in study drug arm). The events were assessed over a 12 month period. Degarelix was used in a different regime in that study (patients received it 7 out of 12 months) and hence not directly comparable to the licensed dose regimen. None of the studies were designed to capture cardiovascular events as a formal end point and all events were recorded as adverse events. All risks and events were recorded by oncologists and not cardiologists. The cardiovascular events were recorded as a composite including cerebrovascular events and death. He noted the final conclusion of the authors of the paper that these findings need confirmation in randomized controlled trials. He added that this was a post hoc analysis and not based on trial design. Hence the Committee and ERG considered these as interesting observations but not robust enough to be included as an evidence basis of guidance. Hence, given the lack of robust evidence, they had no choice other than to consider the risks of agonists and antagonists as equal.

66. Mr Castle, from Ferring, said that Ferring had presented additional evidence to the Committee prior to the FAD.

67. Dr Davey, from Ferring, added that the Committee and ERG should have considered the totality of evidence and comments from consultees, and had they done so it would not have been reasonable to act as the Committee did.

68. Prof. McVeigh, on behalf of the Appraisal Committee, reminded that the Committee was not required to consider additional evidence presented prior to the FAD. However, they had indeed considered the additional evidence provided by Ferring and experts, but had not been convinced by it.

69. The Appeal Panel considered these points. The Appeal Panel unanimously concluded that the Appraisal Committee reviewed the available evidence in detail

and considered it appropriately. The Committee had also considered additional evidence, which it was not required to consider. The Panel understood that evidence for reduction in cardiovascular risk based on the submitted trials is limited and was not the primary focus of any of the trial data presented. The Appeal Panel decided that the conclusions derived by the Appraisal Committee were indeed reasonable in the light of the evidence available.

70. The Appeal Panel, therefore, unanimously dismissed both these appeal points.

Conclusion and effect of the Appeal Panel's decision

71. The Appeal Panel therefore upholds the appeal on two ground 1a points.

72. The Appeal Panel upholds the appeal on Ferring Point 1.1a, (*which is materially the same as Tackle Prostate Cancer Point 1.1a, and the British Uro-Oncolgy Group point 1.1a*): NICE failed to issue a second ACD following a substantial change to the preliminary recommendations that significantly reduces the number of eligible patients that can be treated with degarelix.

73. The Appeal Panel also upholds the appeal on Ferring Point 1.2a *(which is materially the same as Tackle Prostate Cancer Point 1.2a):* The decision in the FAD to restrict use of degarelix to patients with spinal metastases who have actual spinal compression (as opposed to those who are "at risk" of spinal compression) lacks transparency and fails to give adequate reasons

74. The appeal is dismissed on all other grounds.

75. The appraisal is remitted to the Appraisal Committee who must as a minimum issue an ACD to consult on the wording currently in the FAD. If the Committee wishes to review that wording in advance of a consultation and in light of some of the issues discussed at the appeal and consult on a new formulation that is a matter for it. The Appeal Panel notes that the language for patients "at risk of spinal cord compression" or "impending" or "signs & symptoms" of has been used in unhelpfully loose ways. The Panel suggests that a future ACD should be precise in its language and any term used must be clearly defined (not just referenced to another guideline) and consistently and exclusively used to describe the group defined. The Panel suggests that the definition of the patient group should be very clear, not reliant on different interpretations of language, and capable of application in a routine clinical setting.

76. 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 publishing the final guidance.