Single Technology Appraisal

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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The appeal letters are available on the NICE website here

1. **Final Draft Guidance** issued for appeal in July 2023

2. **Appeal panel outcome**

3. **EAG scenario analyses addendum** prepared by Liverpool Reviews and Implementation Group (LRIG)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Voxelotor for treating haemolytic anaemia caused by sickle cell disease

1 Recommendations

1.1 Voxelotor with or without hydroxycarbamide is not recommended, within its marketing authorisation, for treating haemolytic anaemia caused by sickle cell disease in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with voxelotor that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

Usual treatments for haemolytic anaemia caused by sickle cell disease include hydroxycarbamide (also known as hydroxyurea) or regular blood transfusions. There is an unmet need for effective treatments for sickle cell disease, and health inequalities affect people with the condition.

Clinical evidence suggests that people who have voxelotor are more likely to have an increase in haemoglobin levels compared with people who have usual treatment. Although this is likely to be beneficial, the trial population did not align with the company's proposed second line population or the company's economic model. So how well voxelotor works in the company's proposed second line positioning is uncertain because:

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- the key trial was short, so it is uncertain what the benefits are in the long term
- the people in the trial did not reflect the people who would have voxelotor in the NHS at the company's proposed second line positioning, because they were not able to have regular blood transfusions and did not have to have had hydroxycarbamide previously.

The cost-effectiveness estimates for voxelotor are also uncertain. This is because some assumptions used to estimate the cost effectiveness were not supported by clinical trial evidence.

Voxelotor has the potential to address the health inequalities associated with sickle cell disease and the unmet need for effective treatments, so a higher cost-effectiveness estimate could be accepted for decision making. But, the estimates for the company's proposed second line positioning were extremely uncertain. Any estimate that could be considered sufficiently reliable for decision making would likely be above what NICE considers an acceptable use of NHS resources.

It was not possible to assess voxelotor use with managed access because the company did not provide a managed access proposal. So voxelotor is not recommended.

2 Information about voxelotor

Marketing authorisation indication

2.1 Voxelotor (Oxbryta, Pfizer) is indicated for 'treatment of haemolytic anaemia due to sickle cell disease in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for voxelotor.

Price

2.3 The list price of voxelotor is £5,917.81 for a 90-pack of 500 mg tablets (excluding VAT; BNF online accessed June 2023). The company has a commercial arrangement, which would have applied if voxelotor had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 In sickle cell disease (SCD), a gene mutation causes red blood cells to become irreversibly sickle shaped. These cells are then broken down in a process called haemolysis, which causes haemolytic anaemia, resulting in low haemoglobin levels. The patient experts explained that the symptoms of haemolytic anaemia in SCD include pain, fatigue, weakness, tachycardia, dizziness and confusion. Sustained haemolytic anaemia can affect the function of multiple organs, causing organ damage, strokes, sight loss and other symptoms, which substantially affects quality of life. The patient experts described how normal everyday activities can be difficult for people with haemolytic anaemia. They explained that some symptoms can lead to sickle cell crises, which needs hospital treatment multiple times a year. This can have a considerable impact on work and education, as well as on carers. The pain resulting from SCD has a major impact on quality of life. There can be constant background pain making day-to-day life uncomfortable, in addition to episodes of excruciating debilitating pain that has been described as more painful than childbirth. Maintaining social relationships and employment can be difficult because of the complications resulting from SCD. For most people with SCD, the clinical course of the disease is uncertain. This can be a source of anxiety

for people with SCD and their parents or carers. The patient experts also explained that SCD is not widely understood, including among healthcare professionals, which can result in poor care and further anxiety. The clinical experts explained that some of the long-term morbidities in SCD are directly related to the degree of haemolytic anaemia. One clinical expert highlighted that a potential complication related to low haemoglobin levels is cerebral damage in children and young people with SCD. They considered that increasing haemoglobin levels in people with haemolytic anaemia would mean fewer hospital admissions, reduced risk of symptoms and organ damage, improved mental health and less time off work or education. However, the committee noted this association was not reflected in the HOPE trial. The patient experts also explained how SCD has a substantial impact on people with the condition from an early age, and on their carers. They explained that transitioning from childhood into adulthood can be particularly challenging, including learning how to manage the condition themselves. They also commented that navigating work and social life is particularly difficult for people with SCD. In response to consultation, the clinical and patient experts further highlighted that people with SCD face health inequalities and there is an unmet need for this population. The committee acknowledged the substantial difficulties and health inequalities faced by people with SCD. It recognised that SCD is a serious condition that can affect the body across multiple organ systems, can impact the mental wellbeing of people with the condition and their carers, and is associated with considerable morbidity.

Clinical management

Treatment options

3.2 Usual treatment for SCD includes ensuring adequate hydration, preventing infections and treating pain, with or without hydroxycarbamide. Regular blood transfusions may also be considered. The patient experts explained it is also important to avoid triggers when managing SCD. These include cold weather, stress and physical activity. They gave an

example that temperature variance between rooms in a house can lead to crises and so it is important to ensure the house is a consistent temperature throughout. The patient and clinical experts explained that there are limited treatment options for SCD. A patient expert described their experience of taking hydroxycarbamide for 20 years after starting it as a child. Initially it was effective, but as they got older and their weight increased, the dose of hydroxycarbamide also increased up to a maximum amount. When they reached adulthood, hydroxycarbamide was no longer as effective, even at the maximum dose. Hydroxycarbamide also cannot be used during pregnancy or by people trying to conceive. So they moved to another treatment option, crizanlizumab, in line with NICE's technology appraisal guidance on crizanlizumab for preventing sickle cell crises in sickle cell disease, and reported this to be helpful so far. The committee was aware that crizanlizumab is not a comparator in this appraisal. The patient and clinical experts commented that there is a lack of innovation and investment in treatments for SCD and an unmet need for an effective and well-tolerated treatment that can be taken over a lifetime. The clinical experts also commented that it is unknown if voxelotor has an impact on fertility because there is no long-term data or trial data. The company explained there is no data on voxelotor's impact on male fertility and only some real-world evidence of voxelotor use in pregnancy. The committee noted the All-Party Parliamentary Group's No One's Listening report, which highlighted health inequalities experienced by people with SCD and inadequate investment in the condition. The committee concluded that there is an unmet need for effective treatments and health inequalities affect people with SCD. It noted people with SCD would welcome a new treatment that addresses the short-term symptoms and long-term complications of haemolytic anaemia and improves their quality of life.

Population

3.3 In its submission, the company positioned voxelotor as 'second-line treatment after hydroxycarbamide in people who are ineligible for,

intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective'. In response to consultation, the company updated its proposed positioning by removing the term 'unwilling to take hydroxycarbamide'. The committee was aware that this would mean voxelotor would be used as monotherapy when people cannot have or are intolerant of hydroxycarbamide, or as combination therapy when hydroxycarbamide has not worked well enough on its own. It noted that the company's proposed population was narrower than the marketing authorisation indication, and therefore narrower than the population in the NICE scope (that is, people with SCD). It also noted that the company had not submitted evidence for a possible subgroup of interest identified in the NICE scope, defined as 'combination treatment with or without hydroxycarbamide'. The HOPE trial included people who had previously taken, were taking and who had never taken hydroxycarbamide. The EAG noted that 64% of people in the voxelotor arm and 63% in the placebo arm were taking hydroxycarbamide at baseline. The company confirmed that most people continued to take hydroxycarbamide throughout the HOPE trial. The EAG commented that the population in the HOPE trial was not limited to people having voxelotor as second-line treatment, and HOPE did not represent the company's proposed positioning of voxelotor. The company explained its positioning of voxelotor as a second-line treatment after hydroxycarbamide has been offered, was chosen after consultation with 9 UK clinicians. The clinicians stated that this is the most likely position for its use in the NHS. The committee recalled that the HOPE trial excluded people who were having regular transfusion therapy. But in the company model, regular transfusion therapy was included at different rates for each arm (see section 3.9). It therefore noted the company's proposed positioning of voxelotor as a second-line treatment was not aligned to the population in the HOPE trial. So it may be more appropriate for the company to position voxelotor as a first-line treatment option for SCD, in line with its marketing authorisation. The company explained that the British Society of Haematology recommends hydroxycarbamide as a first-line treatment, so it would

expect voxelotor to be used as a second line treatment. The committee acknowledged the guidelines but felt that this did not prevent the possibility of voxelotor displacing current standard care. In response to consultation, clinical experts highlighted that voxelotor may be particularly beneficial for a specific subgroup of people with SCD. That is, people with severe anaemia (haemoglobin level less than 6 g/dl), who are unable to have transfusions and whose condition has not responded to hydroxycarbamide or they do not tolerate it. The committee asked the company whether there is any evidence for the clinical effectiveness of voxelotor in this subgroup. The company stated it is difficult to generate evidence in this subgroup and was not aware of any available evidence. The committee concluded that the company's proposed second-line positioning was not supported by trial evidence. Also the trial population did not represent the company's proposed population in NHS practice or in the company's economic model. It further concluded that the company had not robustly explored the use of voxelotor in populations aligned with the HOPE trial and the marketing authorisation, in which it would be used as a monotherapy or as combination therapy. The committee also recognised there may be a specific subgroup of people with SCD who might particularly benefit from voxelotor. But, it was not presented with any evidence to allow exploration of the clinical effectiveness and cost effectiveness of voxelotor in these populations.

Comparators

3.4 The comparator in the company's cost-effectiveness analysis was established clinical management without voxelotor. It was defined as 1 or more of supportive care, hydroxycarbamide and regular blood transfusions. The clinical experts explained that all people with SCD should be offered hydroxycarbamide as first-line treatment. But some people cannot have hydroxycarbamide or choose not to have it because of the risk of side effects and possible impact on fertility. For this group, the clinical experts said they would consider treatment with voxelotor. The committee noted that people are unlikely to be 'unwilling' to take a

clinically effective treatment without reason. It asked the patient experts if this would be better phrased as 'ineligible or intolerant', especially if it related to areas such as contraindications because of pregnancy. The patient experts said that many of the reasons driving patient choice would be issues such as effects on fertility and pregnancy. But, there were some people who would choose not to take it even if it was not contraindicated, because of worries about the potential side effects. Some people also have concerns related to hydroxycarbamide being a cancer treatment. The committee sympathised that these factors could make people reluctant to use hydroxycarbamide, and that this must be especially difficult in the context of having so few treatments available. But it would be unusual to completely rule out a potentially clinically effective and medically indicated comparator for these reasons. The committee concluded that it was important to distinguish between people with medical contraindications to hydroxycarbamide, and people who chose not to take it for other reasons. In response to consultation, the company updated its proposed positioning by removing the term 'unwilling to take hydroxycarbamide'. The committee asked the clinical experts whether, if voxelotor was recommended, they would continue to use hydroxycarbamide at first line, and which treatments voxelotor would displace. The clinical experts stated that they would not offer voxelotor and hydroxycarbamide together as an initial treatment. And that for now they would continue to offer hydroxycarbamide before voxelotor, apart from for a small subset of people with very low haemoglobin levels, although they didn't specify the level of haemoglobin. The committee understood from this response that clinical practice may change in future, which added more uncertainty about voxelotor's likely line of therapy in the NHS (see section 3.3). And so the most appropriate comparator was also uncertain. The committee noted that there was also a therapeutic benefit from regular transfusion therapy (see section 3.12) and that the company had proposed that voxelotor would reduce the need for regular blood transfusions. This suggested that regular blood transfusion was also a potential comparator, but was excluded in the HOPE trial (see section

3.5). In response to consultation, the company outlined that an indirect treatment comparison between voxelotor and regular blood transfusions would be useful. But it explained that this was not feasible because of lack of data. The EAG agreed with the company. The committee further noted the company's proposed positioning was ill-defined and did not match the trial population because in this positioning, voxelotor could be used as monotherapy or combination therapy (see section 3.3). The eligible population and therefore the comparator for voxelotor monotherapy and combination therapy remained unclear. Taking everything into account, the committee concluded that the most appropriate comparator was uncertain. But it was likely to be either hydroxycarbamide or regular transfusion therapy or a mix of both, and this may differ depending on whether voxelotor is used as monotherapy or in combination.

Clinical effectiveness

Data sources

3.5 The clinical evidence was based on HOPE, a phase 3, double-blind, randomised, placebo-controlled trial of voxelotor compared with placebo. The population was people with SCD who had a haemoglobin level of between 5.5 g/dl and 10.5 g/dl. The trial was done in 60 centres in 12 countries over 24 weeks. It had a 72-week follow up, during which treatment was given. Hydroxycarbamide was allowed in both arms of the trial. Acute rescue transfusions were also allowed, but people having regular blood transfusions were excluded. The primary outcome was the percentage of people with a greater than 1 g/dl increase in haemoglobin at 24 weeks. In the voxelotor 1,500 mg arm of HOPE, 51.1% of people had a greater than 1 g/dl increase in haemoglobin at week 24 compared with 6.5% in the placebo arm. This difference was statistically significant. No treatment effect was observed with voxelotor on the exploratory endpoints reflecting disease burden, which included quality of life, rate of opioid use and percentage of people who required rescue transfusions of red blood cells. The clinical expert explained that people with haemoglobin levels below 6 g/dl would be considered to have severe

anaemia and would need treatment in addition to hydroxycarbamide. The committee noted the mean haemoglobin levels at baseline in HOPE were 8.6 g/dl in both arms, so were higher than 6 g/dl and not reflective of a population in whom hydroxycarbamide is not effective enough. In response to consultation, the company explained that hydroxycarbamide is not indicated for the treatment of haemolytic anaemia and so haemoglobin levels alone are not used to determine whether hydroxycarbamide is effective. The committee concluded that the population in HOPE did not represent the company's proposed NHS practice population or the population in the company's economic model (see section 3.3).

Treatment effect

3.6 The HOPE trial showed a statistically significant difference for voxelotor compared with standard care in the number of people who had an increase in haemoglobin of at least 1 g/dl at week 24. The committee noted that this was a surrogate outcome, and considered whether it was meaningful for people with haemolytic anaemia in SCD. The patient experts commented that this increase in haemoglobin for people with SCD could provide a considerable benefit. They explained that the lifestyle of people with SCD is determined by the level of anaemia, and an increase of at least 1 g/dl in haemoglobin may improve symptoms and function. One patient expert advised that when their haemoglobin increased in general, they were able to work full time rather than part time, and were able to exercise more and live a healthier lifestyle (the amount of haemoglobin increase was not stated). The clinical experts also shared their experience of using voxelotor in the early access to medicines scheme. They explained the clinical effect of an improvement in haemoglobin with voxelotor occurs within 1 to 2 weeks. They said that for people with SCD, an increase of 1 g/dl in haemoglobin would likely substantially improve symptoms and quality of life. And this effect would be expected to occur across the range of haemoglobin levels seen in SCD, for example it raises baseline haemoglobin so people are better

able to tolerate any exacerbations of disease. They acknowledged that the measured haemoglobin concentration simplifies complex changes in the make-up of circulating blood, which differ according to the reason for a haemoglobin rise (for example, whether it is caused by transfusion, voxelotor or natural variation of the disease). The committee concluded that an increase in haemoglobin of 1 g/dl is likely to be beneficial for people with SCD, despite there being no significant change in quality of life shown in the trial evidence (see section 3.14). However, it acknowledged some uncertainty over whether the benefit may vary depending on the mechanism causing this increase in haemoglobin.

Long-term complications

3.7 The HOPE trial provided data over 72 weeks, and the HOPE open-label extension trial provided data over a further 48 weeks. The EAG noted that HOPE did not provide evidence for the long-term impact of voxelotor on the development of SCD complications. HOPE also showed no significant difference between voxelotor and placebo for some short-term outcomes, including the proportion and total number of vaso-occlusive crises, health-related quality of life and the proportion requiring an acute transfusion. The company explained that HOPE was not designed for this. The clinical experts noted it was difficult to determine whether voxelotor will reduce long-term complications and there is currently no clinical evidence for this. But they explained that long-term complications of SCD can be a result of either vaso-occlusion or chronic haemolytic anaemia. Because voxelotor increases haemoglobin levels, they expected voxelotor would reduce the risk of long-term complications caused by haemolytic anaemia. The clinical experts also noted that there is a lot of 'silent damage' caused by haemolytic anaemia in SCD, with the chronic nature of the disease resulting in end-organ damage. They reported that there is increasing evidence that having chronic haemolytic anaemia affects areas such as cardiac function (because the heart must work harder) and bone density. The committee acknowledged the challenges of providing long-term evidence that voxelotor reduced long-term complications. But it was

aware that the NICE manual for health technology evaluations states that when using a surrogate outcome, there should be good evidence that the relative effect of a technology on the surrogate endpoint is predictive of its relative effect on the final outcome. This evidence would preferably come from randomised controlled trials, or if that is not possible, epidemiological or observational studies. In response to consultation, the company highlighted that the link between lower haemoglobin levels and poorer outcomes is biologically plausible and is demonstrated across epidemiological studies. It noted this corresponds to a level 2 surrogate relationship according to the NICE manual for health technology evaluations. The committee recognised it was clinically plausible that voxelotor could reduce long-term complications in SCD, but because of the lack of evidence, there were high levels of uncertainty around the nature and extent of any effect.

Economic model

Company's modelling approach

3.8 The company submitted a discrete event simulation model to estimate the cost effectiveness of voxelotor compared with standard care for treating haemolytic anaemia in SCD. Possible events in the model occurred on a time-to-event basis. The committee considered that, methodologically, a discrete event simulation model was a valid approach to estimate the cost effectiveness of medicines. It is a sophisticated approach that allows the incorporation of disease history and competing risks, and the committee appreciated the company's efforts in developing this. But given the highly uncertain assumptions feeding into the model (see sections 3.3 and 3.4, and sections 3.6 to 3.14), many of the advantages of this more sophisticated approach were lost when modelling the cost effectiveness of voxelotor. The added complexity of this model may have led to more uncertainty than using a more traditional modelling approach, by combining more modelling complexity than usual with more uncertain assumptions than usual. At the first committee meeting, the committee

concluded that the company's modelling approach added uncertainty to the results. It suggested the company could consider either a more straightforward modelling approach, or use its existing model to more fully explore the uncertainties in the underlying assumptions (see sections 3.6 to 3.14), population modelled (see section 3.3) and comparators (see section 3.4). In response to consultation, the company did not update its modelling approach. But, it did provide scenario analyses varying the rate of regular transfusion therapy with standard care (see section 3.10) and the utility benefit associated with a 1 g/dl increase in haemoglobin (see section 3.14). The EAG noted that although these scenario analyses were useful, they did not resolve the uncertainty in the underlying assumptions. The committee noted the scenario analyses helped to quantify the uncertainties to an extent. But it concluded that there remained substantial uncertainty around some of the inputs used in the economic model because they were not supported by clinical trial evidence. The EAG noted that real-world evidence might help reduce these uncertainties. The committee recalled that the company did not provide an evidence submission or economic model in a population aligned with voxelotor's marketing authorisation. The company also did not provide clinical trial evidence for voxelotor in its proposed second line positioning (see section 3.3) The committee concluded that the company's economic model and proposed second line positioning did not reflect the population in the HOPE trial, meaning that the clinical and cost effectiveness of voxelotor in the company's second line positioning could not be robustly assessed.

Regular transfusion therapy

3.9 The company model included considerably different rates of regular transfusion therapy at baseline for the voxelotor and standard care arms (the exact proportions of people needing regular transfusions in both arms are considered confidential by the company so cannot be reported here). The company explained that there was no clinical trial data to inform the rates and so the estimates for both arms were generated from a modified Delphi panel exercise with 9 English clinicians specialising in SCD. The

proportion in the standard care arm was derived from a weighted average of the responses. The proportion in the voxelotor arm was derived from a consensus among the 9 clinicians. The EAG was concerned about this methodology. It thought the company should have at least assumed the same rate in both arms or, preferably, modelled the risk of needing regular transfusion therapy at baseline. The committee was not clear why rates of regular transfusion therapy varied substantially at baseline in the model, given the lack of supporting evidence. The company explained this was based on results from the modified Delphi panel. The committee was aware the section 3.3 of the NICE manual for health technology evaluations states that evidence generated by expert elicitation is subject to risk of bias and high uncertainty. In the company's response to consultation, it explained the difference in the regular transfusion therapy rates between the 2 arms. It said this was because people in the voxelotor arm had voxelotor after hydroxycarbamide treatment, instead of regular transfusion therapy. The company added that it was not a result of people already having regular transfusion therapy switching to voxelotor. The committee noted that the different proportions of people having regular transfusion therapy in each arm at baseline was a main and substantial driver of the cost-effectiveness estimates. It also recalled that acute one-off rescue transfusions were allowed in the HOPE trial but regular transfusion therapy was excluded (see section 3.3), so there was no trial evidence for the proportion of people who have regular transfusion therapy with voxelotor or standard care. The committee was concerned that the evidence used to inform the proportions of people having regular transfusion therapy in the model was uncertain. The committee noted it had not seen any clinical evidence of a difference in the proportion of people who have regular transfusion therapy between voxelotor and standard care. It was also concerned that the company had used 2 different approaches when choosing the values for the 2 arms. This resulted in the value for voxelotor being based on the lower end of the range given by the Delphi panel (because the company asked for a range,

and also asked for clinical consensus on the most likely value in that range). Whereas, the standard care arm was based on an average of the range (in its submission the company did not report whether it had asked for consensus on the most appropriate value in that range). In response to consultation, the company explained that the same opportunity was given to discuss and review their answers in the standard care arm, but a consensus was not reached. So it used a weighted mean of the range for the rate of regular transfusion therapy with standard care. The committee noted the company explanation, but it was aware of the large variance in the estimates provided by the modified Delphi panel. It concluded the methodology and results from the modified Delphi panel exercise were uncertain and resulted in assumptions that were more favourable for voxelotor.

Regular transfusion therapy with standard care

3.10 In response to consultation, the company provided results from an expert consultation done with 9 UK haematologists. The consultation took place between March and April 2023 and set out to estimate the rate of regular transfusions that people have with standard care. The consultation estimated a higher rate of regular transfusions than the rate used in the company base case. The company also provided an estimated rate of regular transfusion therapy with standard care based on consultation with UK clinicians from 2020. This was lower than the rate used in the company base case (the exact rates are considered confidential by the company so cannot be reported here). The company explained that the regular transfusion therapy rate with standard care from the modified Delphi panel in the company base case is a reasonable estimate, lying between the different clinical expert estimates. The EAG acknowledged the difficulties in estimating the regular transfusion rate with standard care and felt that the company preference for the rates from the modified Delphi panel was reasonable based on the data presented. The committee noted the estimate from the modified Delphi panel was highly uncertain. But, it considered the alternative rates provided by the

company helped to reduce this uncertainty. The committee concluded that although the rate of regular transfusion therapy with standard care remained uncertain, it should be based on the rate from the company's modified Delphi panel. Nevertheless, this did not negate its concerns over the differential rates used for standard care and voxelotor (see section 3.9).

Regular transfusion therapy with voxelotor

3.11 In its response to consultation, the company did not provide alternative assumptions for the rate of regular transfusion therapy with voxelotor in the model. The EAG highlighted that the rate of regular transfusion therapy accounted for a substantial proportion of the total treatment costs in the standard care arm, compared with the vastly reduced proportion of total treatment costs in the voxelotor arm (the exact proportions of total treatment costs in both arms are considered confidential by the company so cannot be reported here). In the absence of further evidence, the EAG provided scenario analyses to explore the uncertainty. In these scenarios, the rate of regular transfusion therapy with voxelotor was based on values from the company's modified Delphi panel. The EAG used the highest value provided in the modified Delphi panel and an average of the lowest and highest value. It also provided a scenario in which the rate of regular transfusion therapy with voxelotor was equal to the rate with standard care. The committee recalled that the HOPE trial excluded regular transfusion therapy and so the results from HOPE do not show a difference in the proportion of regular transfusion therapy between the arms. It recognised it may have been suitable to exclude regular transfusion therapy in the HOPE trial because of the risk of confounding, because the primary outcome of HOPE was the percentage of people with a greater than 1 g/dl increase in haemoglobin (see section 3.5). This meant there was no clinical trial evidence to support the rates of regular transfusion in the model, including whether it was appropriate to assume different rates of transfusion at baseline with voxelotor compared with standard care (see section 3.9). The committee noted that in the scenario

analyses provided by the EAG, varying the rate of regular transfusion therapy with voxelotor had a substantial effect on the cost-effectiveness estimates. It was aware the company did not present clinical evidence for the rate of regular transfusions with voxelotor and the value provided by the company was highly uncertain because it was generated from a small number of clinical expert opinions in the modified Delphi panel. It also noted that the company provided other possible sources for the rate of regular transfusion therapy with standard care. This helped reduce the uncertainty. But, it did not provide other possible sources for the rate of regular transfusion therapy with voxelotor. The committee noted the rate of regular transfusion therapy with voxelotor was a major driver of the cost-effectiveness results and that the values were not based on clinical trial evidence but on clinical opinion from only 1 source, the modified Delphi panel. Given the extremely high uncertainty of this value, and its large impact on the cost-effectiveness results, the committee was unable to determine the most appropriate estimate for the rate of regular transfusion therapy with voxelotor. It recognised the uncertainty around this rate may be reduced through the collection of longer-term data in the NHS through a managed access agreement. However, it noted that it was not presented with a managed access proposal from the company. So the committee was unable to explore this further.

Haemoglobin benefit after regular transfusion therapy

3.12 In its submission, the company assumed in its model that after regular transfusion therapy, people have an increase in haemoglobin compared with baseline (the exact increase in haemoglobin used is considered confidential by the company so cannot be reported here). This was based on analysis of real-world evidence from the Symphony database in the US 28 days after a transfusion (the exact increase in haemoglobin from Symphony is considered confidential by the company so cannot be reported here). The company received clinical advice that regular transfusion therapy involves a transfusion every 6 weeks and that any increase in haemoglobin declines 3 weeks after a transfusion. So the

company halved the value from Symphony. The EAG commented that the value from Symphony was for haemoglobin levels 4 weeks after transfusion. So a haemoglobin increase at 3 weeks should be at least as high as the value at 4 weeks. It therefore preferred to use the value from Symphony for the increase in haemoglobin in people who have had a transfusion. The clinical expert commented that they would expect people with SCD who have regular transfusion therapy to have a therapeutic benefit and an improvement in their quality of life after a transfusion. They also explained that after a transfusion, the increase in haemoglobin is likely to be higher than the company estimate. In response to consultation, the company highlighted that it would expect the mean change in haemoglobin after transfusions in Symphony to be higher than in the UK. It explained that the UK uses automated red cell exchange therapy more frequently than the US which uses top-up transfusions. It commented that automated red cell exchange therapy does not increase overall haemoglobin concentration as much as top-up transfusions. So the mean change in haemoglobin from the US Symphony database is likely to be higher than that from the UK. But the company did update its model to assume a haemoglobin increase after a transfusion based on the Symphony data. The committee recognised the uncertainty relating to the haemoglobin increase after a transfusion. But, based on the evidence it was presented and clinical expert opinion, the committee concluded that the amount of haemoglobin increase after a transfusion should be based on the Symphony data.

Time-to-event probabilities

3.13 The company's model included estimates of future complications, such as acute renal failure, arrythmias, gallstones, heart failure, stroke and vaso-occlusive crises. To do this, the company linked haemoglobin levels from HOPE with SCD complications using data derived from the UK Hospital Episode Statistics Clinical Practice Research Datalink (HES-CPRD) database. This database provides data on people using primary and secondary healthcare. The company also provided a scenario analysis

using the US Symphony data. The EAG noted that the HES-CPRD database only provided data for 2,106 people and that the population was not aligned with the HOPE trial inclusion criteria. That is, the HES-CPRD database included people who had 3 or more confirmed secondary care interactions for SCD before baseline haemoglobin measurement, and not all of the people included had a vaso-occlusive crisis during the previous 12 months (the exact percentage of people is considered confidential by the company and so cannot be reported here). In HOPE, all the participants had at least 1 vaso-occlusive crisis during the 12 months before enrolment. The committee noted that the mean age in the HES-CPRD database was higher than the median age of 24 years in HOPE, and that the licensed population that was 12 years and over (the exact mean age in HES-CPRD is considered confidential by the company so cannot be reported here). So, the HES-CPRD database may not be representative of the age in HOPE or the licensed population. The EAG was also concerned about the company's methods of generating time-to-event probabilities. It explained that the company used 1 index haemoglobin level at a specific time point to determine the time-to-event probabilities. The EAG explained it would prefer an analysis that shows how changes in haemoglobin levels affect the probability of experiencing a complication. In response to consultation, the company applied the inclusion criteria for vaso-occlusive crises events from HOPE to the HES-CPRD database, to better match the HOPE trial population. The EAG commented that the company revision better aligns to the HOPE trial population, but it does not address the uncertainty around nature and extent of raising haemoglobin levels on long-term SCD complications. The committee agreed that the updated company time-to-event analysis using HES-CPRD data better matched the HOPE trial population. It also reflected on its previous conclusion that although there may be some impact of reducing haemoglobin on future complications, this relationship was highly uncertain. It concluded that this added further uncertainty to the model.

Utility values

Source of utility values

3.14 In the HOPE trial there was no significant difference in EQ-5D score between the voxelotor and standard care arms at 72 weeks. The company stated that, although it was not necessarily challenging the use of the EQ-5D as a tool for SCD, it was concerned that it may not have been used effectively in the trial. At technical engagement, the company had also stated that there was little research testing the validity of the EQ-5D for SCD. It noted there was missing EQ-5D data from HOPE at 72 weeks, and that baseline EQ-5D values in HOPE were higher than expected for people with SCD. It also commented that the impact on long-term complications on quality of life was not captured in HOPE. Instead of using direct HOPE trial data, the company used an analysis of EQ-5D data from the Patient Journey Survey of people with SCD to assess the relationship between haemoglobin levels and quality of life. Using linear models of utility as a function of haemoglobin, the company estimated a utility benefit per 1 g/dl increase in haemoglobin and applied this benefit in the model for both arms (the exact utility benefit is considered confidential by the company so cannot be reported here). The patient and clinical experts also commented that the EQ-5D may not capture the true quality of life in people with SCD. They noted that it is a chronic, lifelong condition and so it can be difficult for people with SCD to put into perspective how much the disease impacts their life. The committee recalled the clinical expert's expectation that there would be an improvement in haemoglobin within 1 or 2 weeks after treatment with voxelotor (see section 3.6). The committee noted that EQ-5D values from earlier in the HOPE trial did not show a significant difference between the arms. Furthermore, it noted that the European Medicines Agency stated 'no beneficial effect of the treatment was observed between groups on endpoints that reflect disease burden and patient wellbeing'. However, the committee recalled the patient expert's statement that an increase in haemoglobin of 1 g/dl could have a substantial impact on quality of life (see section 3.6). It also

acknowledged that the experts considered that the trial may not have accurately captured quality of life in SCD, which caused uncertainty. The committee recognised the uncertainty in the clinical evidence. But it noted this could be reduced by exploring alternative approaches, such as:

- reviewing whether the EQ-5D scores from HOPE consist of unusually high numbers
- obtaining EQ-5D scores from other sources (for example, vignettes), or
- exploring an alternative health-related quality-of-life measure (for example SF-36, which has a longer recall period than EQ-5D).

In response to consultation, the company attempted to exclude EQ-5D scores from HOPE that were higher than general population scores at baseline. But, it explained the data set was too small and not qualitatively different from what had already been presented. It highlighted an improvement in quality of life associated with voxelotor as demonstrated by improvements in the Clinical Global Impression of Change from HOPE. In the voxelotor arm, 74% of people were described as 'very much improved' or 'moderately improved' compared with 47% of people in the placebo arm. It also did a literature review to explore alternative approaches to capture the impact of a 1 g/dl increase in haemoglobin on quality of life. The literature review identified studies in disease areas other than SCD, such as chronic kidney disease, iron deficiency anaemia and anaemias related to cancer. It provided a range of utility benefit between 0.0114 and 0.109 associated with a 1 g/dl increase in haemoglobin. The company explained that the range identified from the literature review reinforced the uncertainty around the utility benefit associated with a 1 g/dl increase in haemoglobin. So to explore the uncertainty, it provided scenario analyses using utility benefits of 0.028, 0.075 and 0.109 associated with a 1 g/dl increase in haemoglobin. Because its base case utility value fell within the range identified in the literature review, the company maintained its original base case utility value. The committee recognised that an increase in haemoglobin of

1 g/dl was likely to be associated with an improvement in quality of life for people with SCD and therefore a utility benefit in the model. But it noted the exact utility benefit was highly uncertain. It recalled that the HOPE trial showed no statistically significant difference in EQ-5D between the 2 arms. It noted the dimensions of EQ-5D include activities of daily living and self-care which were identified by the patient expert as benefits from reduced fatigue after treatment with voxelotor. So quality-of-life benefits of voxelotor should have been detected within the EQ-5D measurements in the HOPE trial. It also recalled comments from the patient and clinical experts that a 1 g/dl increase in haemoglobin may have a substantial impact on the quality of life of someone with SCD. The committee noted the scenario analyses provided by the company and EAG, which confirmed changing the utility value in the model had a minor impact on the cost-effectiveness results. The committee also noted it had not been presented with other plausible utility values for a 1 g/dl increase in haemoglobin specifically in people with SCD. The committee concluded that the utility benefit in the company base case from the Patient Journey Survey of people with SCD is suitable for decision making. It reached this conclusion based on:

- no other plausible utility values being presented for a 1 g/dl increase in haemoglobin in people with SCD
- the minimal impact on cost effectiveness and
- the clinical and patient expert testimonies.

But the committee highlighted this value is very uncertain and understood that health-related quality of life can sometimes be difficult to capture for people with chronic conditions from an early age (see section 3.16). It would have preferred to see alternative health-related quality-of-life values in people with SCD or an alternative quality-of-life measure used in HOPE, such as SF-36.

Costs

Resource use

3.15 The committee noted that in the company model, costs for adverse events associated with SCD were sourced from NHS reference costs 2019/20. It particularly highlighted the costs included in the model for surgical procedures. It recognised that people with SCD who need a surgical procedure must have a blood transfusion to increase their haemoglobin levels before surgery. The committee noted that the costs of blood transfusions were not included in the surgical procedure costs, and so the model may underestimate these costs.

Severity

Quality-adjusted life year weighting

3.16 In its submission, the company explained that haemolytic anaemia in SCD is a severe condition. People with SCD have a range of acute and chronic complications, including progressive organ damage and the associated symptoms and comorbidities. The patient and clinical experts also stated that haemolytic anaemia in SCD is a debilitating condition with symptoms and complications that can negatively impact quality and length of life. The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. The company provided absolute and proportional quality-adjusted life year (QALY) shortfall estimates in line with NICE's health technology evaluations manual. Absolute QALY shortfall is the future health lost by people with a condition, including quality and length of life, compared with the expected future health of people without the condition, over their remaining lifetimes. Proportional QALY shortfall represents the proportion of future health that is lost by people with the condition, including quality and length of life. The committee noted that the company's own base case and EAG's absolute QALY shortfall calculation results were below 12, and their proportional QALY shortfall calculation results were below 0.85 (the exact figures are confidential and so cannot be reported here). In response to consultation,

the company accepted that its model did not produce QALY estimates that met the formal quantitative eligibility criteria for severity weighting. But it considered that voxelotor should qualify because the calculation had not fully captured the severity of SCD. The company highlighted that the average age of people in the model was 27.58 years, which meant that the assessment of disease severity had not captured the lifelong burden of disease before entry into the model. It also explained that the QALY loss for people with SCD could be greater than estimated in the model. This is because people who have chronic conditions from an early age have been shown to adapt to their levels of disability. So, paradoxically, they then report better quality of life than would be expected. NICE's health technology evaluations manual clearly stipulates that eligibility for the severity modifier should be based on future rather than past health loss. The committee recognised the impact of the condition (see section 3.1), and it agreed that the model had not fully captured the lifelong nature of the condition. It noted that the characteristics of the population in the company's model did not reflect the populations in the marketing authorisation or the HOPE trial. For example, the populations in the marketing authorisation and the HOPE trial were younger than the population in the model. The committee recognised that SCD can have a substantial impact on people with the condition and their carers. It was disappointed that the model did not adequately capture the population that would have this treatment in NHS practice. It recalled that even the company's own base case did not meet the threshold to allow a QALY weighting to be applied and so concluded it was unable to apply the 1.2 QALY weighting.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 Because of confidential discounts for voxelotor and other treatments included in the model, the exact cost-effectiveness results are commercial in confidence and cannot be reported here. The company base case

incremental cost-effectiveness ratio (ICER) was below the range that NICE considers an acceptable use of NHS resources, and the EAG's exploratory estimates were substantially above the range. The committee recalled the considerable uncertainty around the evidence for multiple model parameters in the company base case and that some of the assumptions were not supported by clinical evidence. It noted it was not presented with clinical trial evidence for the positioning of voxelotor and that the economic model used clinical opinion for some important inputs. It particularly highlighted the uncertainty of the evidence base for the proportion of people needing regular transfusion therapy in the model. The committee noted that the model was highly sensitive to the rates of regular transfusion therapy and that even a small change in the rates used in the company's base case had a substantial upward effect on the ICER so that it was no longer within the range normally considered a cost-effective use of NHS resources. This was illustrated by the company's and EAG's scenario analyses. Increasing the rate of regular transfusion therapy with voxelotor (see section 3.11) or decreasing the rate of regular transfusion therapy with standard care (see section 3.10) resulted in ICERs that were substantially above the range that NICE considers an acceptable use of NHS resources. The committee also commented that the population in the company model included considerably different rates of regular transfusion therapy in each arm. This was not aligned with the HOPE trial population, in which regular transfusion therapy was excluded. So the trial population did not represent the company's proposed population in NHS practice or in the company's economic model (see section 3.3). It recalled that the company's proposed population was narrower than the marketing authorisation (see section 3.3). It also recalled the rate of regular transfusion therapy with voxelotor and the different proportions of people having regular transfusion therapy in each arm at baseline substantially affected the cost-effectiveness results and were highly uncertain (see sections 3.9 and 3.11). Because of the substantial uncertainties associated with some of the model inputs, the

committee concluded that the company's and the EAG's cost-effectiveness estimates were subject to high levels of uncertainty that could not be resolved without further data collection. The committee concluded the company's economic model and proposed second line positioning did not align with the population in the HOPE trial, meaning that the clinical and cost effectiveness of voxelotor in the company's second line positioning could not be robustly assessed. It was disappointed that the high levels of uncertainty about the population and model inputs meant that it could not adequately assess the cost effectiveness of voxelotor, given the historic challenges associated with SCD.

Other factors

Equality issues

3.18 The committee considered potential equality issues raised by the company, experts and patient groups:

- SCD is not widely understood, including among healthcare professionals, which often results in poor healthcare and stigma around seeking pain relief for crises.
- The condition is more common in people from African, Caribbean, Middle Eastern and South Asian family backgrounds, and as a group these people tend to have poorer health outcomes in the UK than people from other family backgrounds.
- There is a high unmet need and limited access to new safe, effective treatments for SCD, which widens health inequalities for the SCD community.

The committee discussed each of the equality issues raised. It noted that any recommendation for voxelotor would be unable to address the issues related to poor healthcare and stigma around seeking pain relief, and that these were beyond the remit of a technology appraisal. It also acknowledged the potential health inequalities faced by people with this

condition and was mindful that the principles that guide the development of NICE guidance and standards included the aim to reduce health inequalities. The committee noted that SCD is mostly seen in people from certain family backgrounds, and recognised that these groups experienced worse health outcomes and barriers to treatment. It also noted the All-Party Parliamentary Group's inquiry report findings of serious health inequalities associated with SCD. The committee was hugely grateful to the patient experts for their testimonies about living with the disease. The committee acknowledged that health inequalities affect people with SCD. It concluded that it was willing to take health inequality into account in its decision making by accepting a higher cost-effectiveness estimate than it otherwise would have done, despite the considerable unresolved uncertainty (see section 3.20).

Innovation

3.19 The company considers voxelotor to be innovative because it is the only approved treatment that addresses sickle cell haemoglobin polymerisation. Voxelotor is a once daily oral treatment, which has advantages compared with regular transfusion therapy, which needs frequent hospital appointments, can damage veins over time and sometimes needs iron chelation to reduce the risk of iron toxicity. The company also considered that voxelotor will reduce the need for transfusion-related hospital visits. The committee considered comments from patient groups highlighting the limited research and development in SCD compared with other orphan diseases. It agreed there was an unmet need for this population. It also noted its previous conclusion that the model may not have fully captured the severity of the disease. It recalled that the NICE health technology evaluations manual states that the committee should use the most plausible ICER as the primary consideration when making decisions about the acceptability of a technology as a cost-effective use of NHS resources. But, if there are strong reasons to suggest that the health benefits of the technology have

been inadequately captured and may therefore misrepresent the health utility gained, this should be taken into account (see section 3.20).

Conclusion

Recommendation

3.20 The NICE health technology evaluations manual states that consideration of the cost effectiveness of a technology is necessary but is not the only basis for decision making. The committee was willing to be flexible, taking into consideration the significant unmet need for effective treatments in SCD, and NICE's aim of reducing health inequalities (see section 3.18). It concluded it would accept a higher cost-effectiveness estimate for decision making than it otherwise would have done to address such health inequalities, despite the considerable unresolved uncertainty. But it noted that departing from NICE's usual range needs to be done with caution, as it displaces funding from what may be more cost-effective treatments elsewhere in the NHS, with an overall net loss of health gain (see the principles that guide the development of NICE guidance and standards). The committee noted that the HOPE trial population did not represent the company's proposed population in NHS practice or in the company's economic model. It noted it was not presented with clinical trial evidence for the company's proposed positioning of voxelotor and that the economic model used clinical opinion for some important model inputs, so the evidence provided for multiple parameters in the model was highly uncertain. It recalled that small changes to these assumptions resulted in a substantial increase in the ICERs. So, despite being willing to be flexible by accepting a higher cost-effectiveness estimate than it otherwise would have done, and to consider potential uncaptured benefit, it concluded that the cost-effectiveness estimates were not suitable for decision making and that any plausible ICER was highly uncertain but likely to be substantially above the range NICE considers an acceptable use of NHS resources. So it concluded that voxelotor could not be recommended for routine use.

Managed access

3.21 Having concluded that voxelotor could not be recommended for routine use, the committee considered if it could be recommended with managed access for treating haemolytic anaemia in SCD. The committee recalled that to consider a recommendation with managed access, the committee need a managed access proposal from the company along with a feasibility assessment from NICE. The draft guidance produced after the first committee meeting stated that voxelotor could be a promising new medicine, with potential resolvable uncertainty, and may be a candidate for managed access. Although the company expressed that it would be open to discussing the possibility of managed access, it did not make a managed access proposal for voxelotor. The NHS England Innovative Medicines Fund clinical lead commented that, as a result, it is not clear whether a period of managed access could sufficiently resolve the remaining clinical uncertainties. At the second committee meeting, the company explained it had not submitted a managed access proposal because it believed the additional data provided in response to consultation and an updated patient access scheme had reduced the uncertainties to a level that would permit a positive recommendation. It further explained that the additional data needed to resolve the remaining uncertainties would not be generated through a period of managed access. The committee noted the company's reasons for not submitting a managed access proposal. The committee recalled the rate of regular transfusion therapy with voxelotor and the different proportions of people having regular transfusion therapy in each arm at baseline substantially affected the cost-effectiveness results and were highly uncertain (see sections 3.9 and 3.11). It commented that some of the major uncertainties in the model, in particular the rate of regular transfusion therapy with voxelotor, may have been reduced after a period of managed access. But it noted that it had not been presented with a managed access proposal with a feasibility assessment to explore if new evidence could be collected without undue burden on the NHS. After clarifying with the company that

no managed access proposal had been submitted at any point, the committee concluded that it was unable to consider a recommendation with managed access.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Nigel Gumbleton

Technical lead

Caron Jones and Carl Prescott

Technical advisers

Kate Moore

Project manager

ISBN: [to be added at publication]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]: Decision of the panel.

Introduction

1. An appeal panel was convened on 13 October 2023 to consider an appeal against NICE's final draft guidance (FDG) to the NHS on voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403].

2. The appeal panel consisted of:

- Professor Jon Cohen Chair
- Dr Biba Stanton Health service representative
- David Tyas Industry representative
- Rosemary Harris Lay representative
- Dr Justin Whatling Non-executive director of NICE

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

4. The appeal panel considered appeals submitted by Pfizer and the Sickle Cell Society (SCS).

5. Pfizer was represented by:

- Emma Clifton-Brown Head of Value and Access

- Lucy Richardson — UK HTA Sub Team Lead for Rare Diseases
- Dr Oliver Shastri — UK Medical Team Lead for sickle cell disease
- Sarah Love — Legal representative
- Professor Mark Layton — Clinical representative

6. SCS was represented by:

- John James — Chief Executive
- Professor Paul Telfer — Clinical Representative
- Dr Arne de Kreuk — Clinical Representative
- Tinu Williamson-Taylor — Patient Representative
- Kalpna Sokhal — Patient Representative

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

- Dr Megan John — Chair, technology appraisal committee D
- Giles Monnickendam — Committee member
- Linda Landells — Associate director
- Nigel Gumbleton — Technical adviser
- Dr Jacoline Bouvy — Programme director

8. The appeal panel's legal adviser, Amy Smith (DAC Beachcroft LLP), was also present.

9. 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.

10. 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.

11. Dr Mark Chakravarty, NICE Lead non-executive director for appeals, in preliminary correspondence, had confirmed that Pfizer had valid grounds for appeal under Ground One and Ground Two and SCS had valid grounds for appeal under Ground One.

12. The appraisal that is the subject of the current appeal provided advice to the NHS on voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403].

13. The numbering of appeal points in this letter 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 submissions from Pfizer, SCS and the committee for the points that were discussed relevant to the decisions of the panel.

14. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: John James on behalf of SCS, Emma Clifton-Brown on behalf of Pfizer and Dr Megan John on

behalf of NICE. Tinu Williamson-Taylor also provided her testimony and experiences of sickle cell disease and voxelotor for which the appeal panel is very grateful.

15. The panel were very grateful to both Tinu Williamson-Taylor and Kalpna Sokhal for their moving accounts of their lived experience of sickle cell disease and voxelotor.

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

Pfizer appeal point 1a.1: It was procedurally unfair for the committee not to give, at any point during the appraisal process, any indication of what it considered to be the plausible cost-effectiveness of voxelotor.

16. The appeal panel chair, acknowledged Pfizer's appeal point 1a.1 and appeal point 2.1 cover similar territory. He noted they would be taken individually as they needed to be approached from different perspectives but there may be some overlap in discussion across both points.

17. Sarah Love, for Pfizer, explained that both point 1a.1 and point 2.1 are focused on the committee's decision not to give an indication of cost-effectiveness, how unusual that was, whether it was explained adequately or at all, and whether it made sense with reference to the modelling and context. Sarah Love noted that this was inconsistent with Pfizer's past experience of NICE appraisals.

18. Sarah Love explained that what procedural fairness requires varies from case to case, that procedural requirements may arise from a statutory process or legitimate expectation, and that this is context specific. She stated that the basic requirements of fair consultation must be followed. These include that those affected (such as SCS, patients and Pfizer) are consulted at a formative stage, given enough information and time to provide a properly informed response and that

the response must be conscientiously taken into account. Sarah Love said nobody should be “on the back foot”, for example addressing new information at the last moment or wondering what assumptions have been relied on, or feel that they are presented with a *fait accompli*. If flexibilities are shown or a particular approach is taken in previous appraisals then parties will reasonably expect to be treated similarly in future appraisals or, if there is a change in policy such that NICE does not offer the same opportunities, this should be communicated in good time. Sarah Love stated she would not expect a different approach on a basic matter such as expressing a view on cost-effectiveness unless there was a very good reason.

19. In regard to reasonableness, Sarah Love explained that it is not enough for the appeal panel to disagree with the committee's view, it must be shown to be unreasonable. The question is not whether it strikes her but whether it strikes someone with clinical or health economic modelling expertise as obviously wrong. Sarah Love explained that she emphasised this because there were several points about which committee expressed uncertainty, and the panel could come away with an impression of there being a difference of opinion, but the Pfizer consider it to be much more than that: the concerns the committee have expressed do not make sense to Pfizer and, rather than a difference of opinion, cause Pfizer surprise and bafflement.

20. Emma Clifton-Brown, for Pfizer, noted that she had been involved in 14 appraisals in the last three and a half years. In each of those appraisals the committee provided their preferred assumptions and a most plausible Incremental Cost Effectiveness Ratio (ICER) or ICER range. The decision by the committee not to provide a most plausible ICER or ICER range was unprecedented in Pfizer’s experience and Pfizer did not understand why it was not possible to provide an ICER

or ICER range for voxelotor. She accepted that there were uncertainties but stated that this appraisal was not so unique or different from other appraisals as to warrant no ICER. Like the majority of appraisals, this one was based on a randomised control trial; the modelling was accepted by NICE and enabled assessment of the impact of inputs on the ICER. Emma Clifton-Brown noted the committee concluded that cost effectiveness was substantially above the acceptable range but was unable to provide an ICER. She said section 6.2.34 of NICE health technology evaluations: the manual (the Manual) allows the committee to accept higher levels of uncertainty which could be factored into the ICER. Pfizer assumed that the committee had ICERs in mind and had Pfizer been given an ICER, even if uncertain, it would have made a huge difference to how Pfizer responded and a material difference to the outcome of the appraisal.

21. Dr Megan John, for NICE, referred to section 5.8.64 of the manual and stated that the committee was obliged to give an ICER only when applicable. She explained that the committee was unable to provide an ICER or ICER range due to the uncertainties in the evidence which meant no calculated ICER was more plausible, reasonable or rational than another.

22. Linda Landells, for NICE, explained that it was important to note that committees do not always produce an ICER at the draft guidance stage. There were plenty of examples where a committee has concluded that the evidence was too uncertain to provide an ICER or ICER range. She explained that the difference here was that usually the consultation process would allow for an ICER or ICER range to be produced which could be used in decision making. That was not the case in this appraisal. Where the foundations of the ICERs produced are not acceptable there is no point in putting forward a number or range that cannot be trusted.

23. Dr Megan John said nobody should be surprised by the conclusions in final draft guidance. She considered it difficult to see from the papers that anything should have been a surprise to Pfizer. The committee clearly outlined the uncertainties which meant it was unable to produce an ICER and the onus was on Pfizer to respond to the issues outlined, but this was not forthcoming.

24. Giles Monnickendam, for NICE, said that not providing an ICER was somewhat unusual but was certainly not unprecedented. The reason why the committee took the approach it did was that there was an unusually high degree of uncertainty. He explained there were three substantial areas of uncertainty which led to the committee's approach. The first was around how an improvement in the short-term surrogate outcome (increased haemoglobin levels) would translate to reduced long term complications of sickle cell disease. The next was the extent to which improvement in haemoglobin levels would result in short term health related quality of life improvements. The third was the extent to which voxelotor could replace regular transfusion therapy (RTT) in the target population whilst also maintaining short term and long-term effectiveness, which was a critical area. He explained that the first issue whilst uncertain resulted in a relatively small impact of less than [redacted] incremental quality adjusted life years (QALYs) in the model and was not a major driver. Although an important uncertainty, the committee considered this uncertainty could be acceptable in the decision-making and found ways to accept it in the model. The second issue had a moderate impact on the ICER but following patient input the committee was willing to accept the uncertainty and included that impact in the model. However, the third issue was the real sticking point. The extent to which voxelotor could effectively substitute for RTT was extremely uncertain. It was also a main driver of the ICER. The plausible range of RTT rates generated a range of incremental costs that resulted in

more than a thirteen-fold increase in the ICER. This very wide ICER range was not useful for decision-making. Within the range the committee was unable to determine any ICER value that was more plausible than another as there was no reliable evidence to inform their choice. This was further exacerbated by a number of factors including structural issues in the modelling and fundamental issues with the target population and evidence used to parameterise the model from the HOPE trial. He said the model represented an oversimplification of the clinical pathway. Taking all of these factors into account the committee did not feel comfortable to state a most plausible ICER or ICER range that could be considered a reliable representation of the uncertainty and be used for decision making.

25. Dr Jacoline Bouvy, for NICE, stated that it was not unusual for no cost-effectiveness value to be provided after the first appraisal committee meeting (ACM1). This tends to be where there are structural uncertainties and problems with the model or evidence that goes into the model. What is unusual in this appraisal is that the uncertainties were not addressed by or at the second appraisal committee meeting (ACM2). Dr Bouvy explained that the draft guidance identified the issues with the evidence and model and the analyses that were required for the committee to assess plausible cost effectiveness of voxelotor. Pfizer were provided with additional time to address these issues and provide additional analyses at ACM2 but, unusually, Pfizer did not provide these analyses. This left the committee in an unusual position at ACM2 that it was unable to change its position as the issues in the draft guidance had not been addressed.

26. In response to a question from the appeal panel as to whether it considered there to be any statutory obligation on NICE to provide an ICER, Emma Clifton-Brown and Sarah Love, confirmed they were not

aware of any obligation in legislation and this appeal was based on Pfizer's previous experience of the norm.

27. In response to a question from the appeal panel as to whether Pfizer had requested the committee to provide them with the most plausible ICER after ACM1, Lucy Richardson, for Pfizer, explained that Pfizer only acquired the technology and became involved in the appraisal after ACM1. Lucy Richardson explained that she was aware conversations had been held between the previous manufacturer and NICE regarding thresholds and how to address potential uncertainties. She said the fact that the external assessment group (EAG) had run scenario analyses shows they were trying to get to a most plausible cost effectiveness number.

28. In response to a question from the appeal panel, Lucy Richardson said that Pfizer considered each of the uncertainties identified by the committee and did provide clarifications around a few uncertainties, especially the population and positioning and additional evidence on RTT rates for the standard of care arm, ahead of ACM2.

29. Dr Oliver Shastri, for Pfizer, noted that Pfizer's appeal letter provides a summary of the 7 uncertainties and steps taken to address them by ACM2. Dr Shastri also noted that it was apparent at ACM2 that the committee had concerns regarding the lack of randomised control evidence. He explained that even with the generous extension provided by the committee from the usual 2 months to 6 months between the ACMs, it would not have been possible to run a randomised controlled trial in this time to address the committee's concern.

30. In response to a question from the appeal panel regarding the wording of the FDG (in which the committee concluded they could not provide an ICER due to the uncertainty but notwithstanding this the

ICER was too high to be considered cost-effective for the NHS), Dr Megan John explained that there were many ICERs generated most of which were significantly above what would be an acceptable threshold for the NHS. She explained that there was no evidence to suggest one ICER was more plausible than another, the majority were above the threshold and the committee did not have any confidence in providing one number above another. Dr John said it was difficult to understand how the committee's concerns had only become apparent to Pfizer at ACM2, when these had been discussed in the slides and presentation at ACM1 and the draft guidance that Pfizer and stakeholders were able to respond to.

31. Linda Landells said that the committee had noted these issues as early as the decision problem stage when NICE meets with Pfizer about the approach to the appraisal and technical engagement.

32. In response to a question from the appeal panel regarding why an ICER or even an ICER range was not provided, e.g. confidentiality and/or uncertainty, Dr Jacoline Bouvy said that the reason was uncertainty; the committee did not land on a range because there was not just parameter uncertainty, which created a wide range of likely values for assumptions, there was also structural uncertainty in the model. Dr Bouvy explained that the committee was not confident in the reliability of the model so it could not trust any range the model was generating. This was a key difference in this appraisal compared to many other appraisals where you may have uncertainty but could still rely on the underlying model and evidence as valid, which was not the case here. Giles Monnickendam explained it was critical that the committee had an understanding of what drives the model. He said that to aid this understanding the committee had asked the EAG to conduct scenario analyses in advance of ACM2 (i.e. the EAG scenarios applied to Pfizer base case and labelled as scenario 2a, 2b

and 2c (as reported at slide 28 of the slides for ACM2. The actual values are academic-in-confidence and cannot be reported here). He said it was clear the EAG did not have confidence in the numbers that were produced from the model, but the analysis allowed the committee to understand what was critical for the ICER and decision making. He explained that the scenario analysis demonstrated that the critical assumption was whether voxelotor could replace RTT which was also the assumption which lacked evidence and had a significant impact on the ICER. The appeal chair noted that they had heard that the reason for not publishing ICERs related to uncertainty rather than confidentiality and NICE's view was that notwithstanding they had numbers they were unable to have any confidence in that range of numbers so did not feel it was helpful to provide them.

33. In response to a question from the appeal panel regarding whether the committee explained that this was the key issue to Pfizer, Giles Monnickendam said that through the ACM discussions, information shared, and normal rigorous analysis conducted on its own model he would expect Pfizer to understand the key drivers of their own model. He said it would be clear to Pfizer that the rates of RTT in the voxelotor arm were the major driver of the ICER and if you assumed no effective substitution for RTT the ICER would be extremely high and above the threshold.

34. Dr Megan John confirmed that Pfizer were aware of the uncertainties and their drivers from the ACM1 slides and draft guidance. The committee felt Pfizer took a high-risk strategy by positioning the technology in a place without evidence in support and this was explained to Pfizer at the time.

35. Emma Clifton-Brown confirmed that Pfizer was aware of the uncertainties and the drivers of the model, and the committee was very clear about areas of uncertainty, but Pfizer was not aware that

the committee was not going to accept the additional evidence they provided to help address the uncertainties between ACM1 and ACM2. She said that there were ways to handle this uncertainty, for example, by excluding the RTT data completely. Pfizer put forward the best possible evidence available to supplement the clinical trials and to address these uncertainties.

36. Sarah Love stated that the uncertainties set out at paragraph 3.16 of the FDG were clear at draft guidance stage and these are the areas on which Pfizer has been focussing and did take steps between ACM1 and ACM2 to address these issues. What seemed to have emerged from NICE's comments was that a decision was taken that the numbers were so broad or so high that they were not worth providing to Pfizer. Any numbers, even one excluding RTT, would have been helpful. She could not see why the committee did not give what it had with a “health warning”; there was no reason why an ICER or ICER range was not provided in an appraisal for a community with a high unmet need.

37. The appeal panel concluded as follows. They noted that although the Manual does not expressly require the committee to publish a most plausible ICER, the most plausible ICER is the “primary consideration when making decisions about the acceptability of technologies as a cost-effective use of NHS resources". The Manual acknowledges that there “will be occasions when a range cannot be provided because of existing confidential commercial mechanisms” but does not comment on other situations when providing a most plausible ICER range may not be possible.

38. The panel heard that the committee did not provide a most plausible ICER range in this case because of uncertainty and structural issues with the model. The panel agreed that there was a high degree of uncertainty in this case, particularly in the extent to which voxelotor

would be a substitute for regular transfusion therapy (RTT). The panel understood the committee's position to be that it would be unhelpful to publish an ICER that could not be trusted, and that there was such a large range of potential ICERs that it would not be useful for decision-making.

39. The panel agreed with the view of the appeal panel in the 2020 abiraterone appeal that the “publication of ICER(s) will normally be very desirable both to enable comment during an appraisal and to quality assure guidance when an appraisal is complete.” The panel agreed that if an ICER range were to be so uncertain that it was given no weight in decision-making, then in general there would be no value in providing it. In this case, although the committee clearly had serious concerns about uncertainty in the ICER range, they nevertheless put some weight on the range of ICERs produced through the modelling and analyses in reaching their conclusion. In the FDG, the committee state that “any plausible ICER was highly uncertain but likely to be substantially above the range NICE considers an acceptable use of NHS resources”, suggesting that the committee had ICERs they considered plausible in mind. During the hearing, the NICE committee quoted a range of ICERs that they considered in their deliberations. In particular, they gave a range of ICERs based on a range of RTT rates that they described as “plausible”, albeit that this range was wide. The panel concluded that the NICE committee did have a range of ICERs in mind that informed their decision making. The panel therefore judged that fairness required that this range of ICERs should be provided to stakeholders (with caveats about the degree of uncertainty). The panel was aware that confidentiality may mean that the precise ICERs may not be able to be shared but judged that it was likely that a range could be provided without compromising the confidentiality of competitor pricing.

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

41. The panel noted it would expect NICE to provide the ICERs or an ICER range that informed decision-making. Further, the panel would expect NICE to ensure that stakeholders are able to comment on these and that the committee can consider those observations and whether the guidance should be revised as a result. One way to achieve this would be a further round of consultation.

Pfizer appeal point 1a.2: It was procedurally unfair for the committee not to inform Pfizer, in sufficient time in advance of ACM2, of the estimates generated by the exploratory scenario analyses of the external assessment group ('EAG').

42. Lucy Richardson, for Pfizer, said that the EAG report was shared with Pfizer 10 days before ACM2 which allowed for some concerns to be addressed, however, the issues with cost-effectiveness could only be resolved if the population position and comparators were confirmed. She said that the EAG exploratory analyses had not been seen by Pfizer before this appeal. The ACM2 slides were sent to Pfizer two days before ACM2 which gave insufficient time for Pfizer to comment, especially on the EAG analysis. Lucy Richardson said slide 28 of the slides for ACM2 shows the scenario 2c regular transfusion rate between voxelotor and the standard of care arm. She stated that these analyses made no clinical or logical sense, and Pfizer were provided with no rationale or explanation for the other two scenarios. A committee member questioned why these scenarios were modelled and neither the EAG nor the committee could explain. Lucy Richardson asked how these scenarios had been used by the committee, noting that the FDG only stated that the exploratory estimates were substantially above the range. She said that if Pfizer had received information in sufficient time it could have commented on the accuracy of that information and its appropriateness for decision making. Lucy Richardson questioned why no explanation

was provided of what the additional scenarios were based on and why, even though they contained Commercial Medicines Unit prices, ICER ranges were not provided. Lucy Richardson noted Pfizer anticipated that the impact of confidential prices would have had minimal impact on the ICER. She submitted it was procedurally unfair for the committee to consider these analyses in decision making when there was not sufficient time to ensure they were factually accurate and/or appropriate.

43. Dr Megan John, for NICE, confirmed Pfizer received the slides two days before ACM2 and said this was not unusual. She said Pfizer should not have been surprised given the draft guidance. She confirmed Pfizer did not contact NICE when it received the slides to indicate that more time was needed.

44. Linda Landells, for NICE, confirmed there were no issues of commercial confidentiality. She said the reason this was done was that the committee had previously asked Pfizer to produce the analyses, but it had not. This was why they were produced before ACM2. Linda Landells explained that the purpose of the analyses was to explore and quantify uncertainty around the RTT rates, not to explore the structural uncertainty of the model. She acknowledged that the committee would have ideally shared the analyses with Pfizer with confidential aspects removed. However, due to the complexity of Pfizer model and time available, this was not possible. She confirmed the analyses were run on the committee chair's request following her consideration of the responses to consultation. She explained that the time pressure was due to the nature of what the committee was provided with in response to consultation.

45. In response to questioning from the appeal panel as to why Pfizer did not request more time to review the slides, Lucy Richardson stated it was closer to one day's notice and Pfizer did not have time to prepare

or ask the committee for an explanation before the ACM. She said she had expected to receive the EAG report which would provide details of the scenarios, but this was never received. She reiterated that the report was not available and the first time Pfizer saw this report was in the appeal papers.

46. Linda Landells confirmed that the report had not previously been shared as it contains commercially sensitive information and said the relevant information was included in the slides and that the analyses would not have been difficult for Pfizer to reproduce. She said this was the first time the committee had been made aware of any issues and they were not raised in the ACM nor were any factual issues raised. She explained the information in the slides was not provided at the same time as the EAG report 10 days before the ACM because the analyses had not been run at that point. The analyses were prepared in response to seeing the EAG report. The committee was implicit, if not explicit, in the draft guidance in requesting Pfizer to provide these different scenarios. She referenced paragraph 3.10 of the draft guidance which states, "This could include scenarios in which both arms are equalised at different proportions, and a range of differences in the proportion of regular transfusion therapy across the 2 arms".

47. Dr Megan John further explained that the reason the EAG were asked to run these analyses was because Pfizer had not provided them.

48. Lucy Richardson stated that the scenario analyses could have been shared earlier noting the EAG report was commissioned on 24 May and the committee meeting was not held until the 14 June. She said that Pfizer did not have sufficient time to look at the scenarios and comment on whether they were appropriate to assist the committee with its decision making; if there had been more time Pfizer could have raised questions in the committee meeting or asked for clinical

opinion on the data to understand if the scenarios were actually plausible.

49. In response to questioning from the appeal panel as to why Pfizer did not make representations in ACM2, noting that the analyses were run on information Pfizer had seen before, Emma Clifton-Brown, for Pfizer, said Pfizer were aware of the comments in the draft guidance but had since generated more evidence to show why it was inappropriate to equalise the RTT rates in the two treatment arms. She said it was not until ACM2 that Pfizer was aware of the committee's approach. Pfizer's strategy was to show the committee that this was not the right thing to do in the first place.

50. The appeal panel concluded as follows. During the hearing, there was agreement as to the relevant facts. The committee had hoped that these or similar scenario analyses would be provided by Pfizer between the first and second committee meetings but they were not. The EAG report was shared with Pfizer ten days ahead of the hearing but this report did not include the scenario analyses. The committee chair then asked for these additional scenario analyses to be performed by the EAG, but the model took some time to run. The results were provided to Pfizer in the committee slides two days before ACM2.

51. The panel accepted that sharing committee slides two days prior to the meeting is not unusual, and that this is normally acceptable as a matter of procedural fairness. The panel appreciated that the committee had requested these or similar analyses at the first committee meeting, and that the delay in obtaining them was outside of the committee's control. However, the panel also concluded that these analyses proved to be relevant to the committee's decision-making. The panel understood that the FDG statement that "any plausible ICER was highly uncertain but likely to be substantially

above the range NICE considers an acceptable use of NHS resources" referred primarily to these analyses. In this context, the panel judged that procedural fairness required that Pfizer have an opportunity to scrutinise these analyses. On balance, the panel agreed that two days' notice was not sufficient to allow Pfizer adequate opportunity for scrutiny, and therefore that this was unfair.

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

53. The panel noted it would expect NICE to allow participants in the appraisal to make observations on these analyses, so that the committee can consider those observations and whether the guidance should be revised as a result. One way to achieve this could be a further round of consultation.

Pfizer appeal point 1a.3: In a situation where the committee considered there still to be multiple sources of uncertainty by the time of ACM2, it was unfair nevertheless to proceed directly to the publication of the FDG with no opportunity for a further ACM or to explore suggestions such as managed access.

54. The appeal panel chair explained there are two related but separate points to consider under this appeal point; whether the appraisal should have proceeded to a third ACM; and whether there was adequate opportunity to discuss a managed access agreement (MAA).

55. Sarah Love, for Pfizer, referred to the importance of consistency and transparency in decision making. She explained that it was not necessary to point to a mandatory statement or guarantee in guidance for procedural fairness to require something to happen. She stated that NICE's manual is rightly not prescriptive, allowing the committee flexibility in its decisions. She stated section 5.2.1 of the Manual makes clear it is not possible to set absolute timelines for appraisals. This means there is not a single point beyond which you

cannot have another meeting or do something more to explore uncertainty. She accepted that the Manual states a managed access proposal should be submitted at the evidence stage, but this is not a "must" and multiple touchpoints are mentioned. Although the committee may expect or prefer to receive a managed access proposal by a certain stage this was very different to stopping a company from making a proposal at a later stage, particularly where there were good reasons to focus on routine use and there were uncertainties that could be explored further. Similarly although it might be preferable to have a certain number of meetings, this was different from saying an appraisal cannot proceed to a third ACM if there are further issues still to be resolved after ACM2. She stated the earlier discussion that it was unusual to have no ICER by ACM2 and everyone was working hard to find one was important context. She stated the committee suggest that it was in Pfizer's gift to put forward a managed access proposal and asked therefore whether it was procedurally fair to tell Pfizer on the eve of ACM2 that it could not do so.

56. Emma Clifton-Brown, for Pfizer, said she considered the third ACM and MAA to be intrinsically linked. She said it was not until ACM2 that it became clear there were key uncertainties that required further evidence generation. As this was a complicated appraisal regarding a rare disease with significant health inequalities and no most plausible ICER, it felt unfair to terminate the appraisal without going to a third ACM. When Pfizer saw the slides for ACM2 and it became clear that the committee would not recommend routine commissioning, it was doubly surprising that the appraisal did not proceed to a third ACM so that an MAA could be considered.

57. Emma Clifton-Brown explained that the process was started by another manufacturer who had discussions with the NICE Managed

Access team but considered routine commissioning was the best solution. Pfizer also considered routine commissioning was most appropriate. She said it has been reported that 94% of drugs exiting the Cancer Drugs Fund relied on long term extension data from a pivotal trial, but there was no further data coming from the HOPE trial for voxelotor. Pfizer had looked at real world registry data but was concerned about its ability to resolve uncertainties about the comparative effectiveness of voxelotor. She said Pfizer chose not to provide an MAA proposal for ACM2 despite being asked for one because it expected there would be further opportunities, and the Manual states that an MAA should only be considered if a positive recommendation cannot be made, and a plausible price is required. She said that Pfizer had never taken the position that it was routine commissioning or nothing. She stated it felt unfair for the committee to conclude there was too much uncertainty to provide an ICER at the same time as saying that an MAA to resolve that uncertainty was not an option.

58. Emma Clifton-Brown said applying a cut off for a managed access proposal at that point was unusual and she was aware of 20 appraisal topics in the last 24 months that had proceeded to a third ACM. Given this is a rare disease impacting a population facing health inequalities impacting evidence generation, Pfizer reasonably expected that if the committee was unable to reach a view at ACM2 then a third ACM would be scheduled to inform the decision on routine use or an MAA.

59. Dr Megan John, for NICE, said it cannot be considered unfair not to go to a third ACM because some appraisals do so, as this is not typical and, in this case, was not required as no new issues were identified in the consultation on the draft guidance which would require a third ACM. She said the uncertainties and issues identified

had been subject to full consultation. She said there is an opportunity cost in endlessly appraising the same technology and there is finite resource in the NHS and NICE: there is limited committee time and multiple meetings can prevent other technologies from being evaluated.

60. Linda Landells, for NICE, confirmed that 20 appraisals (as referenced by Pfizer) is around 10% of appraisals going to a third ACM in the last two years, a significant minority. Generally this is when there is new significant evidence submitted at consultation that the committee considers requires further consultation from stakeholders. She said that was not the case in this appraisal. Although the committee was not confident with the ICERs it had carried out its remit within 2 ACMs. She said the Manual provides multiple touchpoints where a managed access proposal can be made, for example, at scoping, submission or technical engagement, and the committee expected Pfizer to make a submission at one of those touchpoints. Targeting routine commissioning did not stop Pfizer from simultaneously submitting an MAA. The committee was flexible and willing to look at a proposal.

61. Dr Jacoline Bouvy, for NICE, said that after ACM2 the committee discussed with Pfizer whether it was appropriate to have a third ACM. In deciding to publish the FDG rather than proceed to a third ACM the committee took into account the finite resources allocated to NICE's work programme and technical team which would be required to support subsequent meetings. This creates an opportunity cost and requires internal resources and committee slots at the expense of other topics. Dr Bouvy noted from a procedural fairness principle the committee was clear after ACM1 what was needed to reach a conclusion on plausible cost effectiveness. The opportunity to provide this information was provided to Pfizer before ACM2. The

outstanding uncertainties and issues were not new so an ACM3 would have prolonged the same discussions, other than potentially considering a managed access proposal. She said the committee explained to Pfizer that there was the possibility of exploring managed access or different positioning through NICE's rapid review process.

62. Emma Clifton-Brown confirmed that Pfizer did request a third ACM and discussed this with NICE after ACM2. She stated that Pfizer recognised the opportunity cost and had offered to pay an additional fee to proceed to ACM3 to get to the fastest outcome.

63. In response to questions from the appeal panel, Dr Megan John said that the committee did not judge that ACM3 would elicit further information to resolve outstanding uncertainties as the uncertainties remained largely the same between ACM1 and ACM2. Given Pfizer had had an extended 6-month period between ACM1 and ACM2 the committee did not expect Pfizer to change its position.

64. Emma Clifton-Brown noted that normally an appraisal would be referred to a third ACM when the company had provided new significant evidence. She said that the reason for delaying ACM2 was due to Pfizer providing new evidence, specifically, the new HES-CPRD study and the Delphi panel. She clarified that this was not a new study but new supporting evidence. She suggested it was unfair not to expect Pfizer to change its position once it understood the committee's view of this evidence.

65. Dr Jacoline Bouvy noted that Pfizer's offer to pay for the third ACM did not assist NICE's limited resources as even if the costs were covered resources would need to be assigned which would postpone another appraisal. It was an important rationale from NICE's perspective that the option of rapid review could be better accommodated into the NICE work programme.

66. In response to a question from the appeal panel regarding whether considering Pfizer's response to the RTT scenarios prepared before ACM2 might have justified a third ACM, Giles Monnickendam, for NICE, said it was clear from the model and draft guidance that the gap between RTT rates in the standard of care and voxelotor arm was what mattered. The committee wanted to see the different extents to which voxelotor could substitute the RTT arm, and Pfizer had not helped to address this issue.

67. In response to a question from the appeal panel regarding Pfizer having confirmed by email that it was not going to submit a managed access proposal, Emma Clifton-Brown reiterated it was focused on routine commissioning and evidence generation and was hoping that if there was any outstanding uncertainty following ACM2 that it could persuade its internal teams to flex on pricing as it has done on previous appraisals. She accepted Pfizer could have submitted a managed access proposal but did not expect managed access to be taken off the table if a proposal was not in place.

68. In response to a question from the appeal panel, Emma Clifton-Brown confirmed that in the pre-meeting for ACM2 a member of the NICE team told Pfizer it was too late to submit a proposal.

69. Sarah Love noted there was still no ICER or ICER range by ACM2 and questioned whether a productive conversation on managed access was possible.

70. In response to a question from the appeal panel, Dr Megan John stated there are no rules preventing a late managed access proposal but there are practicalities to consider and a feasibility assessment is required.

71. In response to a question from the appeal panel as to why NICE told Pfizer it was too late, Linda Landells said she was surprised by Pfizer's position: the draft guidance said the committee was interested in considering a proposal and the committee did not receive one, so it seemed strange that Pfizer wanted to discuss a proposal after ACM2.

72. Dr Megan John reiterated that the committee was open to discussing a proposal following ACM1 which was expressed in the draft guidance, however, the opportunity was not taken by Pfizer. She said Pfizer suddenly changed its mind and the committee could not be sure it would not do so again before a third ACM.

73. Dr Jacoline Bouvy said that one reason why NICE indicated it was too late to make a proposal was because NICE prefer the internal process of a feasibility assessment to be completed before the ACM, so the committee know whether they are able to make a recommendation for an MAA. The committee did have discussions with Pfizer on an MAA proposal following ACM2, and it was suggested this could be considered as part of the rapid review process.

74. In response to a question from the appeal panel as to why exploring an MAA through the rapid review process was not acceptable to Pfizer, Emma Clifton-Brown said that there was no plausible cost effectiveness number to take to an MAA discussion and Pfizer thought the committee's assessment of uncertainty and concerns about the population were wrong. Also Pfizer understood the rapid review process was used to review price and not new evidence, so Pfizer was not clear how rapid review would help.

75. Dr Megan John stated that comments from stakeholders suggested Pfizer had got their positioning and population wrong. She reiterated that appraisals do not routinely go to ACM3 and it is possible to

discuss both routine and managed access commissioning at ACM2, however Pfizer did not provide the committee with this option.

76. In response to a question from the appeal panel as to why the committee could not discuss managed access with Pfizer at ACM2 in the absence of a proposal, Dr Megan John said that she had not refused to discuss it but there was no proposal to consider.

77. Lucy Richardson, for Pfizer, said it was clear in the ACM2 pre-briefing that an MAA proposal was no longer an option.

78. Linda Landells said the potential for an MAA was discussed after ACM2.

79. Emma Clifton-Brown confirmed this was discussed after ACM2 and Pfizer said it was willing to consider managed access as part of a third ACM.

80. The appeal panel concluded as follows. The panel was aware that the Manual does not require a third appraisal committee meeting (ACM), and indeed that having a third ACM is very unusual, but also that the Manual allows flexibility in this regard and that third ACMs are sometimes held. 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 judged that NICE had sought to balance the potential benefits of holding a third ACM with the opportunity costs (in terms of NICE resources that would be diverted away from other technologies). The panel were persuaded by the committee's argument that no *new* uncertainties were identified at the time of the second ACM, and therefore Pfizer had already had a chance to respond to the key areas of disagreement (the positioning of voxelotor and the rate of RTT with voxelotor versus standard of

care). The panel agreed that Pfizer had not made a sufficiently strong case for NICE to take the unusual step of arranging a third ACM.

81. The panel went on to consider whether there had been a procedural unfairness regarding Pfizer's opportunity to submit a managed access proposal. The panel were aware that the Manual affords flexibility about when a managed access proposal can be submitted, but encourages this to be done early in the appraisal process (see paragraph 5.5.21 and 5.5.22 of the Manual). The panel also noted that to consider a recommendation for managed access, the committee needs to receive a managed access proposal and evaluate this. In this case, the committee had suggested at ACM1 that Pfizer submit a managed access proposal, but Pfizer had chosen not to do so. Whilst the panel understood that Pfizer believed a recommendation for routine commissioning was preferable to managed access, this did not prevent Pfizer from submitting a managed access proposal alongside its efforts to generate evidence to support routine commissioning. Both options could then have been considered by the committee at ACM2. In fact, Pfizer raised the possibility of a managed access proposal at the pre-meeting before ACM2. The panel did not agree that the committee had "shut down" the option of managed access at this point: in fact, there was agreement at the hearing that the potential for a managed access agreement was discussed after ACM2. The panel noted NICE had suggested that this could be done using the rapid review process rather than delaying publication of the FDG. The panel judged that both Pfizer and NICE remained open to exploring managed access and that NICE's suggestion that this should be done through the rapid review process rather than by extending the original appraisal was reasonable in the circumstances of this case and was not procedurally unfair.

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

Sickle Cell Society (SCS) appeal point 1a.2: The committee has acted unfairly by including patient and clinical experts in the second appraisal committee meeting only as observers, which meant they were unable to contribute to the meeting.

Pfizer appeal point 1a.4: Given the nature of the outstanding issues, the committee should have ensured that a clinical and/or patient expert was invited to ACM2, to speak directly on issues where their input would have been valuable.

83. The appeal panel chair noted that SCS appeal point 1a.2 and Pfizer appeal point 1a.4 covered similar territory and would be taken together.

84. John James, for SCS, stated the facts were not in dispute: at ACM2 there were no clinical or patient experts, there were still several uncertainties and there was a highly complex set of issues to consider. He said that under those circumstances it was odd and unfair that patient and clinical experts were not allowed to contribute to the debate with a view to addressing and possibly clarifying those uncertainties. He suggested part of the issue under this point is how seriously NICE takes its equalities duties. He challenged Dr Megan John's statement that the committee had all of the information it needed and submitted that, while experts and patients may not have resolved all of the uncertainties, their involvement could have helped in a stand-off between NICE and Pfizer. He noted SCS's patient and clinical representatives had attended the appeal and wished to speak.

85. Tinu Williamson-Taylor, for SCS, provided an account of her experiences taking voxelotor. Tinu Williamson-Taylor noted regular transfusions are not suitable for everyone, and voxelotor provides

another option. She said quantitative analysis confirmed voxelotor improves haemoglobin levels and this improves quality of life in terms of education, school attendance and impact on unfairness and inequality. She asked the appeal panel to consider the bigger picture in a more holistic way.

86. Kalpna Sokhal, for SCS, provided an account of her experiences taking voxelotor. She said health inequalities had been present for a long time and appealed for more resources to go into medication and for NICE and Pfizer to work together to make a positive recommendation. She said that the only options are transfusions or hydroxycarbamide which has to be injected. She said blood transfusions are needed every two weeks and there are additional medications required to manage the side effects.

87. Dr Arne de Kreuk, for SCS, explained that he was a consultant sickle cell specialist and was involved in the HOPE trial. He said that as a clinician he sees examples of patients who have clearly benefitted from voxelotor. He said that voxelotor is an entirely new class of drug with a novel mechanism of action. He accepted that it may not yet be best in class, but expressed concern that if voxelotor is not allowed on the UK market we would lose a valuable opportunity to gather real world data and find out which patients can benefit from this treatment. He said the inequality and patient stories were heart-breaking; it is hard to tell patients there is an effective drug that is not available and explain that the lack of data outside clinical trials prevents access. There is a heart-breaking sense of injustice from patients.

88. Professor Paul Telfer, for SCS, explained that he had been managing people with sickle cell disease for many years and had been involved in most of the development stages of voxelotor. He had been impressed with the effects of voxelotor in some of his patients and considered it should be available for use to help improve quality of life

through better outcomes for patients. He said some patients have no option but voxelotor. He noted concerns as to whether a managed access period would provide the data needed and said that demonstrating long term efficacy is difficult due to the nature of sickle cell disease.

89. Lucy Richardson, for Pfizer, said Pfizer believes experts would have been well placed to comment on the outstanding issues identified by the committee. These included the use and rates of RTT, on which expert views were referenced in the Appraisal Consultation Document (ACD) and expert input would have been valuable. She said Pfizer emailed NICE in advance of ACM2 and were informed that there would be no clinical experts or patient representatives attending the meeting. Pfizer expressed concerns that there were key topics where it was important to hear from clinicians and patients. She said the committee chair explained that verbal input was not required, and that expert/patient opinion would be through reported extracts. Lucy Richardson said it was unclear why the committee thought it was appropriate in the context of inequalities and uncertainties not to try to resolve the outstanding issues without hearing from those best placed to comment.

90. Dr Megan John, for NICE, thanked the patient representatives for their moving testimonies. She said that their experiences were taken very seriously by the committee. The summary of consultation responses was presented in ACM2 but the full consultation comments were in the appraisal papers and considered as part of the committee's decision making. She explained that committee meetings have a very small number of people at the table with a maximum of 2 patient representatives and 2 clinical experts. In consultation the committee received 11 responses, including several group responses and individual patient and clinician responses, so

there was a breadth and depth of responses all of which were considered and taken seriously by the committee. Dr John confirmed that the patient group had the opportunity to provide feedback and did so in their responses during the consultation. She said suggesting there is not equity or parity of esteem between written and verbal comments is problematic.

91. Dr Megan John explained that a NICE appraisal has a beginning, a middle and an end, and ACM2 was normally the end of the decision-making process; the questions included on the slides are for the committee to consider not the stakeholders and experts. These questions were the same as those at ACM1 after which there had been adequate opportunity for stakeholders and experts to voice their opinions through the consultation process. She said that as a GP and human being she hears loudly that health to an individual has no price, but the committee has a duty to all patients not just those who are affected by a positive recommendation of a particular technology. That can feel very difficult but something the committee commits to within NICE's methods and processes and a tax funded envelope.

92. Professor Mark Layton, for Pfizer, echoed SCS's comments about inequalities and unmet need for people with sickle cell disorders. He said that in the past 20 years there had been a single licensed treatment for sickle cell disease commissioned for use in the NHS and it is quite likely that its marketing authorisation may be revoked. He submitted that a clinician expert at ACM2 could have helped dispel confusion on the positioning of voxelotor and the impact voxelotor would have on rates of RTT. He said there is clear evidence that voxelotor would reduce RTT rates and that is borne out by real world evidence.

93. Dr Megan John confirmed that the committee considered written comments only at ACM2 but that patient and clinical experts were present in the room at ACM1, as is the usual NICE process.

94. In response to a question from the appeal panel as to why ACM1 and consultation were insufficient for clinical experts to provide views, Professor Mark Layton, for Pfizer, said there was a focus on the position of voxelotor that would have benefited from a clinical perspective. Dr Oliver Shastri, also for Pfizer added Pfizer believe there was a fundamental misunderstanding by the committee which clinical experts would have helped clarify.

95. In response to a question from the appeal panel as to why the committee did not consider it necessary to invite clinical experts to ACM2 given there were differences of opinion on technical issues like positioning, Dr Megan John explained Pfizer conducted the Delphi panel between ACM1 and ACM2 and the committee also received 11 responses from clinical and patient experts during consultation, including several groups such as the British Society for Haematology. The committee considered it had asked the relevant questions and received a broad depth of clinical opinion. Further, there is a risk in suggesting that verbal contributions at an ACM are held in higher esteem then other types of comment; that would set an uncomfortable precedent.

96. John James emphasised voxelotor predominantly affects a group of people who have a protected characteristic under the Equality Act 2010. He said the committee is dismissing that by saying it has a responsibility to all patients. He accepted Dr John's comment that NICE had a duty to all patients but suggested this undermines NICE's position that it takes the Equality Act 2010 seriously.

97. The appeal panel concluded as follows. The panel had in mind the valuable contribution that patients and clinical experts make to NICE processes. The panel noted that it is not usual practice for patient and clinical experts to attend the second ACM, but that the Manual affords the flexibility to do this when necessary. The panel therefore considered whether patient and clinical experts should have participated in the second ACM in the particular circumstances of this case as a matter of procedural fairness. The appeal panel were satisfied that patient and clinical expert opinion had been sought and taken seriously by the committee prior to ACM2. Experts had been present at ACM1 and participated in the discussion. Many patients and clinicians had contributed to the consultation and all these responses were considered by the committee. The panel were persuaded by the committee's argument that the issues under consideration at ACM2 were very similar to those at ACM1. Expert opinion on the key issues (such as the effect of voxelotor on RTT rates) varied, and the panel agreed that it would have been wrong to give greater weight to one or two experts present at a meeting than to a wide range of experts consulted throughout the process. Overall, the panel judged that the fundamental disagreements between the committee and Pfizer in this appraisal were unlikely to have been resolved by the presence of patient and clinical experts at ACM2. For all of the reasons above the panel concluded that the process had not been unfair.

98. The appeal panel therefore dismissed the appeal on SCS's point 1a.2 and Pfizer's point 1a.4.

Sickle Cell Society appeal point 1a.1: The committee has acted unfairly by declining the nomination of a patient representative, without any communication to the Society that their nomination had been declined.

99. John James, for SCS, confirmed that SCS submitted two patient nominations and deliberately nominated a patient who had been on the voxelotor trial. That patient was not selected for the appraisal and SCS were only informed of this decision by the patient. John James said he accepted that there was a balance in considering nominations and that other organisations and individuals would also be considered in this choice. However, he did not understand the rationale for this decision and was concerned that SCS was not notified directly. He said the decision not to select the patient without any confirmation to SCS was not reasonable, fair or proportionate.

100. Dr Megan John, for NICE, said that she understood John James was copied to the email to the nominated patient which confirmed she had not been selected. She explained that SCS submitted several nominees but gave no guidance in their submission form or testimony suggesting one submission should be selected over another. The committee welcomed all feedback via all methods so where a patient was not invited to attend an ACM the committee would still have and did welcome written testimony from them. NICE usually have 2 patient experts at the meeting so the 2 SCS nominations would have made up the entire patient contingent. Dr John confirmed that the committee was grateful for all responses and she had asked a colleague to contact SCS to encourage this.

101. Linda Landells, for NICE, pointed to a copy of the email sent to the patient representative confirming she had not been selected and noted John James was copied to the email.

102. The appeal panel concluded as follows. The panel noted that NICE asks stakeholder organisations to nominate experts and then selects from the nominations received. The panel heard from the committee that two patient representatives are normally selected. In this case, more than two nominations were received so some had to be

declined. The panel saw the email that had been written to the patient in question to inform her that her nomination had been declined, and noted that this had been copied to John James at the Sickle Cell Society. The panel could therefore see no arguable procedural unfairness in this decision or how it was communicated.

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

Pfizer appeal point 1a.5: The committee unfairly failed to provide adequate opportunity for stakeholders, during the appraisal process, to comment on how it intended to take (or not take) health inequalities in relation to SCD into account in its decision-making and why.

104. Lucy Richardson, for Pfizer, explained that the committee never provided an explanation of how it would modify its approach to the appraisal to give appropriate weight to health inequalities. She explained that after ACM1 Pfizer emphasised the need for transparency so it could comment on the suitability of the committee's proposed adjustments. The committee stated in the ACD that they would account for health inequalities, but they did not explain how. She said the detail, namely that the committee would accept a higher ICER threshold but accept no further uncertainty, was not received until the FDG and the higher threshold was never known. If Pfizer had further details regarding the flexibility and threshold, it could have explored conservative assumptions to reduce the uncertainty further. She said she was confused about how the committee could say they were willing to accept a higher ICER estimate when no most plausible ICER had been identified: this suggested the committee had not taken into account health inequalities in their decision making. She said that by not explaining this NICE had acted in a manner which was procedurally unfair.

105. Dr Megan John, for NICE, stated that the committee absolutely did take seriously its duty to take into account health inequalities and stakeholders and Pfizer had noted during the appraisal that the committee had made specific comments regarding health inequalities. Dr John said no concerns were raised during consultation regarding the committee's approach to health inequalities and the approach taken was consistent with other appraisals both in this disease area and other areas. Dr John agreed with Pfizer that a most plausible ICER was needed to make use of the committee's willingness to be more flexible, but noted that the ICER thresholds are quite clear and transparent in the Manual: an ICER threshold of £20,000 per QALY gained is generally acceptable, rising to £30,000 per QALY gained where the committee can be confident that the risks do not outweigh the benefits. In this case, despite the uncertainties, the committee was willing to accept a higher ICER because of the health inequalities and unmet need. By permitting a higher ICER threshold the committee are accepting a higher level of uncertainty.

106. In response to a question from the appeal panel as to what information they required at the ACD stage, Lucy Richardson said Pfizer was unaware at the ACD stage that the committee was considering a higher ICER threshold, and this was only apparent when the FDG was published. She said that it was important for Pfizer to know how the committee were considering health inequalities at the ACD stage as this would inform what uncertainties Pfizer should be considering and its value proposition in preparation for the next ACM.

107. Emma Clifton-Brown, for Pfizer, said there were different ways that health inequalities could be taken into account. One way would be to accept a higher ICER threshold which would accept a higher level of uncertainty. However, it was unclear to Pfizer that this was the

intention of the committee. Had Pfizer known the committee had major concerns about Pfizer's evidence and wanted Pfizer to put forward conservative estimates but would allow a slightly higher ICER threshold, then Pfizer would have known what it was dealing with.

108. In response to a question from the appeal panel as to why it was insufficient that paragraph 3.20 of the draft guidance states that "the committee concluded that in principle it would be willing to accept an ICER slightly higher than is usually acceptable", Emma Clifton-Brown, for Pfizer, acknowledged this point but said Pfizer did not have clarity as to whether the committee would accept parameters within the ICER that were uncertain.

109. Sarah Love, for Pfizer, said there was a difference between being told a slightly higher ICER would be accepted, without knowing what that was, and being told that was the only adjustment that would be made. That this was the only adjustment did not crystalise until the FDG. Sarah Love said Pfizer's response to consultation stated there was a need for flexibility in the review of the analyses. She said there were other flexibilities beyond a notionally higher ICER threshold that was somewhat academic given there was no ICER.

110. Dr Jacoline Bouvy, for NICE, explained that the ACD did not discuss other possibilities as the committee considered that accepting a higher ICER threshold to take into account the health inequalities was the most appropriate option.

111. Dr Megan John reiterated that it was inherent in accepting a higher ICER that the committee was allowing for more uncertainties.

112. The appeal panel concluded as follows. The panel were aware of the committee's duty to ensure that the decision-making process is transparent. The panel also noted that there was agreement that this

particular appraisal raised substantial and important equalities issues that had to be addressed. The panel noted that the draft guidance document issued to stakeholders for consultation sets out the committee's proposed approach to addressing these issues at paragraph 3.20, stating that "in principle [the committee] would be willing to accept an ICER slightly higher than is usually acceptable". The panel judged that this was a clear description of the committee's proposed approach that was sufficient to allow Pfizer to provide comment on this at consultation. The panel noted Pfizer's comment 12 during consultation says that "there is a need for flexibility on the review of these [cost-effectiveness] analyses given the challenges with rare diseases, particularly sickle cell disease (SCD); without this flexibility, Pfizer are concerned that historic challenges will continue to disadvantage patients living with SCD" but does not indicate that – or set out specifically why - Pfizer believe the committee's proposed approach is inadequate, or what alternatives they would suggest. Overall, the panel judged that stakeholders had been given adequate opportunity to comment on how the committee intended to take health inequalities into account in decision-making.

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

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

Pfizer appeal point 1b.1: The adjustment made by the committee to reflect the health inequalities associated with SCD, while welcome, was inadequate and should not have been so limited in scope.

114. Sarah Love, for Pfizer, stated that Pfizer say the committee needed to do more and take a more flexible approach. She explained this point 1b.1 overlaps with Pfizer's ground 2 points as Pfizer submits that the committee ought (as a matter of reasonableness) to have accepted Pfizer's position at ACM2 that the evidence and model were sufficient

for the committee to generate a most plausible ICER and assess cost effectiveness, so the FDG ought to be remitted to seek to identify that number, regardless of equalities considerations. She noted point 1b.1 was in that sense an alternative appeal point: Pfizer considers the committee took an unreasonable position that was less flexible than other appraisals, but if the panel does not agree then Pfizer consider the duty to make reasonable adjustments was engaged and required the committee to identify a most plausible ICER. Sarah Love stated this was an unusual equalities point as the committee did acknowledge inequalities and indicated a willingness to accept a higher ICER (albeit without making clear how high). This point went to the reasonableness of how equalities issues were handled and whether the adjustment made makes sense. By not giving a most plausible ICER the committee gave with one hand and took away with the other.

115. Sarah Love referred to advice given by the panel's legal adviser and shared with the parties to the appeal (the Advice), which noted that the 2010 Act does not require NICE to do more than what is reasonable in the circumstances, even where this means an identified disadvantage is not reduced or removed. She stated that, whilst not determinative, it was relevant context that the committee's willingness to ‘flex’ the ICER threshold for voxelotor turned out to be futile as there was no ICER to be compared to any threshold.

116. Sarah Love noted the Advice and summarised the principles it set out. She then turned to applying the above principles to this evaluation. She said NICE is a public authority so the duty could apply. She said sickle cell patients have a disability, noting that powerful evidence had been heard and the Equalities Impact Assessment states "People with sickle cell disease may be registered as disabled". As to whether a provision, criterion or practice (PCP) was applied, Sarah Love pointed

to the discussion of uncertainties at paragraph 3.17 of the FDG and said that central themes emerge of a concern about lack of direct clinical evidence on RTT, the difference between the HOPE trial population and those who would receive voxelotor in NHS practice and Pfizer's positioning. She summarised that the committee's view is the model falls so far short that the committee cannot put a number on cost effectiveness. She stated that in taking that approach and not providing a number the committee is applying a PCP.

117. Sarah Love stated that this approach will disadvantage people with sickle cell disease for three reasons. First, this is a relatively rare disease and much rarer than others evaluated through the single technology appraisal (STA) process. Secondly and relatedly, the disease predominantly affects people of African and Caribbean ethnicity. While the duty to make reasonable adjustments only applies in respect of disability, disability is linked to ethnicity in this appraisal: obtaining trial data will be harder for sickle cell disease than other diseases because of its rarity. The HOPE trial was international but small in size and compounded by ethnicity issues mentioned in the All-Party Parliamentary Group's "No One's Listening" report. Sarah Love said the nature of treatment with voxelotor and RTT means a double-blind study is impossible. Given what weighed in the balance was uncertainty in the evidence, it was obvious that people with sickle cell disease were disadvantaged.

118. Sarah Love said that Pfizer appreciates there may be concerns about limited resource and that many patient groups have a disability, but the law requires reasonable adjustments and there are particularities of sickle cell disease meaning that the committee's approach specifically disadvantages them. Sarah Love stated that Pfizer is not arguing that committee had to accept any ICER or to make *any* adjustment to give it a number for cost effectiveness. However, what

Pfizer was advocating at ACM2 was reasonable and the committee ought to have given Pfizer a number.

119. Sarah Love said that paragraph 3.18 of the FDG explains what the committee did, but the FDG does not say whether the duty was engaged and it is not addressed. She noted that NICE's Principles and Strategy for 2021 to 2026 do not impose a duty to make reasonable adjustments but are public statements by NICE as to how it wants to approach things and what flexibilities it should be willing to offer. Sarah Love questioned whether it makes sense for a committee to express real concerns and say it is willing to accept a higher ICER but then decide not to put a number on cost effectiveness. Sarah Love said that this does not seem to reflect the letter or spirit of NICE's public statements.

120. Dr Jacoline Bouvy, for NICE, stated that it was for the panel to judge whether the committee breached its duty under equalities law but put forward two reasons why this was not the case. Firstly, Dr Bouvy drew a similarity to the highly specialised technology (HST) programme. She explained NICE's manual refers to adjustments and that NICE has the HST programme because it recognises that for ultra rare conditions it needs to provide additional flexibility for uncertainty and the ICER threshold as otherwise people with those conditions would probably not gain access to treatments, which would breach the Equality Act 2010. But even in the HST programme there is a threshold above which NICE does not consider an ICER good value for money. It also happens in the HST programme that the committee concludes it cannot identify a plausible ICER because the model is not suitable for decision making, such as in HST20 on selumetinib. That was draft guidance and after consultation a positive recommendation was made in final guidance, but it shows that while there are situations where it will be appropriate to apply additional

flexibility and a higher ICER threshold, as in HST programme, even in that context there is a limit to what committees are willing to accept. Secondly, Dr Bouvy said the reason the committee could not draw a conclusion on a most plausible ICER in this appraisal was it did not feel it could trust the model and the evidence underpinning it. If the committee had applied flexibility and despite those reservations landed on a plausible ICER it would in effect have been lowering the evidence standard. NICE do not want to set a precedent of making decisions based on lower quality evidence for populations who experience health equality issues. It was the choice of Pfizer to position voxelotor where there was not clinical evidence to support it and if NICE had said that is acceptable this would be quite a dangerous lowering of evidence standards that would be disproportionate to what the committee faced here in respect of inequalities. Dr Bouvy explained in the committee's view the flexibilities applied in this appraisal were proportionate and reasonable but landing on a most plausible ICER after the issues unresolved at ACM2 would have been disproportionate.

121. Dr Megan John, for NICE, in response to a question from the appeal panel chair about circularity of adjusting the ICER threshold but not identifying a most plausible ICER, said that the ICER is the tool at the committee's disposal and that there was not an alternative strategy that would support a different approach.

122. In response to a question from the appeal panel, Sarah Love confirmed that what Pfizer wanted was for the committee to conclude that it could give Pfizer a number or range of numbers in respect of the most plausible ICER to enable progress and facilitate discussions around value proposition and managed access. She said there were no doubt other adjustments that would be appropriate in other appraisals for other patient groups, but here the focus is on people

with sickle cell disease who would have benefited from voxelotor and have been disadvantaged by the committee's approach to the evidence. She said Pfizer is not arguing that the committee should rely on “any old evidence” but that it should look at it by reference to the specific disadvantages to people with sickle cell disease. To say the committee would have flexed the ICER threshold but there is no number does not move the debate forward or help Pfizer think in a constructive way to move to a position where patients are accessing the treatment, which is what we all want to achieve.

123. Giles Monnickendam, for NICE, said that the committee had a very big problem with the quality of the evidence and that is what prevented them from specifying a most plausible ICER or range. He stated he could not see how stating an ICER or range would have assisted with inequality issues. The committee had very little confidence in any of the numbers in front of it.

124. Dr Jacoline Bouvy referred to the panel’s question regarding circularity and stated that the committee indicated it was willing to accept a higher ICER threshold in the draft guidance and at ACM1. At that point there was no plausible ICER, but this is not uncommon at that stage. The committee expected additional analyses could have allowed it to land on a most plausible ICER at ACM2, in which case the committee would have been able to specify the higher than usual ICER threshold. Because that did not happen the committee was in an unusual situation in which it was willing to adjust but was not in a position to land on a most plausible ICER.

125. The appeal panel considered this appeal point alongside the Sickle Cell Society's appeal point 1b.1, as to which see below. The appeal panel upheld the appeal on this point, for the reasons set out at paragraphs 131-142 below.

Sickle Cell Society appeal point 1b.1: The committee breached its duties under the Equality Act 2010 by failing to recognise barriers to access and/or take into account health inequalities for patients with SCD and therefore exceeded its powers.

126. John James, for SCS, stated his focus was on how seriously NICE takes its public sector equality duty ("PSED"). He noted the Advice set out the PSED. He emphasised that sickle cell disease predominantly affects groups of black and brown people and stated the question of how NICE works towards minimising disadvantage has been lost in this debate. He stated NICE is almost colour blind in that it says it must look after everyone; he stated he accepts this is the case, but the Equality Act 2010 is there to protect people with protected characteristics. He stated SCS say that the committee's recommendation negatively affected this community. He stated part of NICE's defence is that it did an Equality Impact Assessment (EIA) but SCS's view is that the EIA is flawed because it is contradictory. He noted the higher ICER threshold and asked what other weight was given to health inequalities and what other steps were taken to minimise the impact on the group affected. As to how equalities ought to have affected the decision, he noted the comments from NICE regarding low quality evidence and the risks of relying on this but stated that SCS considered what could have helped were more conversations at ACM2 regarding managed access and other flexibilities. He stated the consequence of the committee's decision in this appraisal was to take matters backwards and increase health inequalities.

127. In response to a question from the appeal panel as to how the committee “went the extra mile” to satisfy its duties under the 2010 Act in light of its reservations about the evidence, Dr Megan John stated that the committee absolutely accept and acknowledge health inequality associated with sickle cell disease. However, the committee

is constrained by NICE's prescribed methods and opportunity costs within the system. Dr John stated she was yet to hear what the committee could do other than flex the ICER threshold. The committee did its best and took equalities seriously. The EIA formed part of the committee's consideration and was not a tick box exercise. Dr John understood that some readers may think a "no" in the EIA should be a "yes" and explained that a "no" was not because the committee did not acknowledge inequality vis-a-vis patients who do not have sickle cell disease. Rather, this was because the committee thought a negative recommendation would not have different impact among patients who have sickle cell disease.

128. Dr Jacoline Bouvy stated the committee did two things. First, it accommodated extra time between ACM1 and ACM2 to give Pfizer an opportunity to generate evidence. It was Pfizer's decision to respond to that in a very limited way that did not change the committee's view on difficulties with the model. Secondly, it was willing to accept an ICER threshold above what NICE usually considers to be a cost-effective use of NHS resources. It was quite rare for a committee to do that. Dr Bouvy said that in itself is going the extra mile as the higher the threshold the more displacement there is within the system, impacting other groups.

129. Linda Landells, for NICE, added that NICE also gave the patient group extra time to respond when they asked for it.

130. John James accepted that extra time was given but stated that this needed to take into account the complexities of the appraisal and that SCS is a national charity of twelve people that cannot operate in the same way as NICE or Pfizer, making it very challenging to put in a complex response. He thanked NICE for the extra time but noted this is not a level playing field as between SCS and NICE and Pfizer.

131. This appeal point was considered together with Pfizer's appeal point 1b.1 during the hearing and in the panel's deliberations. The panel therefore consider both together in this decision letter, whilst ensuring that the distinct legal questions raised are addressed.

132. The panel were aware that sickle cell disease is significantly over-represented in certain ethnic groups, and that people with sickle cell disease have experienced very substantial health inequalities over a long period of time. The panel noted that there are particular challenges in generating high quality evidence in sickle cell disease, for instance because of the greater difficulty in recruiting people from these ethnic groups into clinical trials. The panel did not doubt that the committee had been aware of this and taken it seriously. It went on to consider whether the committee had met its legal responsibilities.

133. The panel considered the public sector equality duty (section 149 of the Equality Act 2010) which provides that NICE must have due regard to the need to eliminate discrimination, and other conduct that is prohibited by or under this Act, and to advance equality of opportunity between persons who share a relevant protected characteristic and persons who do not share it. In doing so NICE must have due regard, in particular, to the need to "remove or minimise disadvantages suffered by persons who share a relevant protected characteristic that are connected to that characteristic". The panel were aware that what amounts to "due regard" depends on the particular circumstances. Here, the panel concluded that this required the committee to give serious consideration to any equalities impacts and how these could be avoided or mitigated. The panel was aware that this duty must be taken seriously, and not merely seen as a "box-ticking" exercise. In this case the panel were convinced, by both the papers and the statements given at the appeal hearing, that this duty

had indeed been taken seriously by the committee. In particular, the panel noted that the response to question 2 of the Equality Impact Assessment drew attention to the “high unmet need in the SCD community and limited access to new safe, effective treatments for SCD which widens health inequalities for the SCD community". The committee had noted the impact on particular ethnic groups and had also specifically considered how this might impact on the ability to generate high quality evidence (including difficulties in recruiting to clinical trials). The committee had not merely noted this, but this had directly informed their decision-making. The FDG explained that the committee “was willing to take health inequality into account in its decision making by accepting a higher cost effectiveness estimate than it otherwise would have done, despite the considerable unresolved uncertainty." In light of the above, the panel concluded that the committee had complied with the public sector equality duty.

134. For completeness, the panel did not agree with the SCS’s argument that the response to question 4 of the Equality Impact Assessment (“Do the preliminary recommendations make it more difficult in practice for a specific group to access the technology compared to other groups?”) was incorrect or inconsistent with other statements in the EIA. The panel understood and agreed with the committee that question 4 was asking whether, within the whole population of people with sickle cell disease, the decision would make it harder for those sharing a protected characteristic to access the technology.

135. The panel therefore concluded that there had been no breach of the public sector equality duty.

136. The panel went on to consider the duty to make reasonable adjustments imposed by Sections 29 and 20-21 of the Equality Act 2010. The panel first considered whether this duty is engaged. The panel agreed that people with sickle cell disease share a disability as

defined under the 2010 Act. The panel then considered whether the committee had applied a relevant “provision, criterion or practice” that put people who share this disability at a substantial disadvantage compared with those who do not. The panel were advised that the definition of a “provision, criterion or practice” is broad, and may include a one-off or discretionary decision. The panel accepted Pfizer's submission that the committee's approach to uncertainty in this appraisal constituted a “provision, criterion or practice” under the 2010 Act. The panel went on to consider whether that approach put patients with sickle cell disease at a substantial disadvantage compared with other patient groups. They were persuaded by Pfizer's submissions on this point and agreed that the committee's approach would do so. The panel therefore concluded that the duty to make reasonable adjustments is engaged.

137. The panel then had to consider whether the committee took reasonable steps to avoid the identified substantial disadvantage. The panel noted that the duty to make reasonable adjustments is a “maximalist” obligation whereby all reasonable steps must be taken. The committee stated in the FDG that “it was willing to take health inequality into account in its decision making by accepting a higher cost effectiveness estimate than it otherwise would have done, despite the considerable unresolved uncertainty”. Where the most plausible ICER lies in relation to the ICER threshold is the primary consideration in decision-making, so the panel judged that this was the main mechanism open to the committee to avoid the identified disadvantage. The usual ICER threshold for a committee to consider a technology a cost-effective use of NHS resources is £20,000-£30,000 per QALY gained. Where there is substantial uncertainty about the most plausible ICER, as in this appraisal, the threshold would normally be at the lower end of this range, depending on the reasons for the uncertainty. As stated in the draft guidance, the panel

heard at the hearing that the committee would have been willing to consider an ICER slightly higher than £30,000 in this case. The panel agreed that this was a significant adjustment to NICE's usual approach.

138. The panel noted the appellants' argument that the committee should have gone further by taking a different approach to considering uncertainty in the data. The panel judged that the ICER threshold itself is the key mechanism for incorporating issues around uncertainty into decision making, so accepting a higher ICER threshold was inherently showing flexibility in the approach to uncertainty. The panel also agreed that the duty to make reasonable adjustments did not require the committee to approve voxelotor irrespective of the ICER, nor did it require the committee to approve voxelotor regardless of the degree of uncertainty in the data.

139. However, the panel was concerned that modifying the ICER threshold was only a meaningful adjustment if a most plausible ICER or ICER range could be generated. The panel did not judge that this required the committee to generate a most plausible ICER or ICER range regardless of uncertainty: it would be unhelpful to provide an ICER so uncertain as to be meaningless for decision-making. But here, the panel did not accept that the committee had found the ICER range so uncertain as to be meaningless (see discussion under Pfizer's appeal point 1a.1, above). With this in mind, the panel judged that the duty to take all reasonable steps to avoid the identified disadvantage should have included providing an ICER range despite the acknowledged uncertainties.

140. The panel were also aware that Principle 9 of the NICE Principles states that NICE will take account of inequalities in its work. They agreed that this requires NICE to identify and give consideration to how to reduce health inequalities. The panel judged that NICE has

done so in this appraisal. The panel concluded that Principle 9 does not impose any duties beyond those imposed under the Equality Act 2010 that have been considered above.

141. The appeal panel therefore upheld both these appeal points, specifically in relation to the duty to make reasonable adjustments imposed by Sections 29 and 20-21 of the Equality Act 2010.

142. The panel noted it would expect NICE to consider whether there are additional steps it could take to make reasonable adjustments for the substantial disadvantage identified for people with sickle disease. This might include providing a range of ICERs that informed decision-making.

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

Pfizer appeal point 2.1: The committee's conclusion that there was too much uncertainty, such that it could not assess the cost-effectiveness of voxelotor, was irrational.

143. Dr Oliver Shastri, for Pfizer, said it was unreasonable for the committee to conclude that there was too much uncertainty to assess the cost-effectiveness of voxelotor and provide Pfizer with a most plausible ICER. Dr Shastri referred to slide 16 of the slides for ACM2 which – under the heading "Committee preferred assumptions and conclusions" – provides a table of the 7 key differences the committee identified at ACM1 between its preferred assumptions and those of Pfizer. Dr Shastri noted that point 7 in the table, the change in haemoglobin (Hb) following regular transfusion therapy to be [redacted], had been accepted by the committee. Point 4, the long-term complications - high levels of uncertainty around nature and extent of any effect, had been reinforced by scientific evidence in literature submitted by Pfizer in ACM2. Dr Shastri explained the positioning of voxelotor as second line (point 1), the model population versus the

NHS population (point 2), the rates of RTT and Pfizer's exploration of alternative assumptions (point 5) and utilities uncertainties, are addressed in appeal points 2.1 and 2.2, but in summary Pfizer say the committee misunderstood them. In regard to point 3, assessing RTT as a comparator, Dr Shastri said it was appropriate to exclude patients receiving RTT from the HOPE trial as this would obviously confound the interpretation of whether increased haemoglobin was due to the transfusion or voxelotor. Dr Shastri said that the combination use of voxelotor and RTT is not appropriate, so it was not appropriate to consider an identical rate as suggested by the EAG. He explained that you cannot do a double-blind study to compare voxelotor and RTT as one is an oral tablet and one an intravenous infusion.

144. Lucy Richardson, for Pfizer, said that with no head-to-head trial data an indirect comparison would have been informative but as the EAG agreed, not possible. She questioned whether the remaining uncertainties are that unique, especially where there is a rare disease, for the committee not to evaluate cost effectiveness. In her experience this was unprecedented, and uncertainties have always been factored into decision making. Even if there was uncertainty regarding positioning and RTT rates which were considered too substantial for the committee to provide an ICER, the committee could have excluded RTT and generated an ICER for the RTT ineligible population for patients on hydroxycarbamide or on no further treatment. This would be equivalent to the placebo arm of the HOPE trial, or subgroup of patients with RTT as a comparator based on real world evidence. Lucy Richardson stated the committee's approach was unusual and she would have expected a thorough explanation why it was not able to put an estimate forward. She believed voxelotor had been treated inconsistently with other technologies.

145. Giles Monnickendam, for NICE, explained that the committee had significant challenges in assessing the cost-effectiveness of voxelotor. He said the big issue for the committee was Pfizer's positioning. This was the reason why the cost effectiveness could not be determined comprehensively, and this was documented in the FDG. He explained that Pfizer had a marketing authorisation for voxelotor as a monotherapy or in combination with hydroxycarbamide, but it did not specify a specific stage in the treatment pathway and neither did the HOPE trial. Giles Monnickendam said there was evidence to support use within the full marketing authorisation population. He said the European Medicines Agency Committee for Medicinal Products for Human Use stated that although the primary endpoint of an increase in haemoglobin was met there was no effect on the disease endpoint or patient health, so there were important uncertainties about the clinical benefit of voxelotor in the full population under the marketing authorisation. Further, he said Pfizer sought an optimised recommendation from NICE that would restrict the recommendation to second line treatment in people for whom hydroxycarbamide was ineligible, intolerant or insufficiently effective. This was highly problematic as it positioned voxelotor as an alternative to RTT which was the basis of Pfizer's ICER. The issue for the committee was the HOPE trial did not compare patients on voxelotor with patients on RTT so there was no clinical evidence to support this positioning. He said Pfizer were advised of these issues by NICE early in the appraisal process, but this remained a fundamental issue.

146. Giles Monnickendam explained that there were already concerns around quality-of-life evidence for voxelotor with issues modelling the long-term complications. The EAG concluded that Pfizer's evidence did not support any benefit from voxelotor other than increased haemoglobin levels during treatment. This is why the committee were unable to determine an ICER. Giles Monnickendam reiterated that in

response to consultation the committee opted to accommodate uncertainty on short term quality of life and long-term complications. This represented an unusual degree of flexibility from the committee which would not normally be so accommodating. However, in the end the committee could not get away from Pfizer's chosen positioning and it remained a substantial challenge in estimating the cost-effectiveness of voxelotor.

147. In response to questions from the appeal panel regarding information provided by Pfizer by ACM2, Giles Monnickendam said this did not impact the wide range of ICERs the committee was looking at. Whilst a number of issues had been resolved, the fundamental issues with RTT remained. He explained that Pfizer did clarify the expected rate of RTT in the standard of care arm which was accepted by the committee but there was nothing new provided on the RTT rates in the voxelotor arm. This was the fundamental issue and driver of the ICER so without it, nothing changed.

148. In response to questions from the panel regarding whether Pfizer discussed removing RTT from the modelling, Lucy Richardson said that the HOPE trial was a representation of the NHS population so from Pfizer's understanding and clarification from clinicians that was the positioning it always wanted to go with and thought appropriate. Pfizer considered including RTT and having voxelotor as an alternative was appropriate, so it was kept in the base case. Pfizer provided scenario analysis regarding the rates of RTT in the voxelotor and standard of care arms so the committee could understand the impact. This evidence was derived from clinicians and the Delphi panel and whilst the committee accepted the evidence for the standard of care arm, they did not accept it for the voxelotor arm.

149. Giles Monnickendam confirmed the committee was not persuaded by the new evidence. He said the naïve indirect comparison was not at

all robust as there was no evidence of impact of RTT on haemoglobin levels. He explained an assumption was built in the model but based on the clinical advice and small amount of data from the Symphony database; in his view it was very weak evidence.

150. In response to a question from the appeal panel as to whether the committee accepted there was a measurable [redacted] in haemoglobin and that this would translate into a clinical benefit, Giles Monnickendam confirmed this was correct and that changes in haemoglobin would be likely to translate to changes in the long term.

151. In response to a question from the appeal panel as to why calculated confidential ICERs that included some that would seem not too far away from what might be considered acceptable by NICE were not worth discussing with Pfizer, even as a range, Dr Megan John, for NICE, stated they could not be shared as there were confidential discounts. Dr John said the committee could not say whether one ICER was more reliable than another. She said it was confirmed in the ACM slides that the ICERs were greater than the normal threshold but that was as specific as the committee could be.

152. Sarah Love, for Pfizer, noted that Pfizer's positioning had been described by the committee as "highly problematic". She said that other issues flow from that and asked if Pfizer was ever told that if they provided a model for a different positioning then the committee would provide an ICER.

153. Dr Megan John said Pfizer was asked and the reason the committee asked the EAG to run scenarios was because Pfizer elected not to.

154. In response to a question from the appeal panel as to whether the committee discussed publishing an ICER range without the RTT variable, Linda Landells, for NICE, said the committee asked Pfizer in

the draft guidance to provide a range of scenarios with varying transfusion rates. Pfizer could have chosen to remove the rates in both arms, but they only provided scenarios varying the rates in the standard of care arm.

155. The appeal panel concluded as follows. Under Appeal Point 1a.1, the panel had concluded that it was unfair that the committee had not provided a range of most plausible ICERs that informed its decision making (see discussion in paragraphs 37-41 above). This appeal point under ground 2 is concerned with whether the committee's conclusion that there was too much uncertainty, such that it could not assess the cost-effectiveness of voxelotor (by providing a most plausible ICER) was unreasonable. The panel considered it was not unreasonable of the committee to conclude that the ICER range was highly uncertain. Nor did the panel think it would have been unreasonable to withhold the ICER range or conclude that it was impossible to assess cost-effectiveness if that range had no bearing on decision-making because of this uncertainty. However, the panel judged that concluding that "any plausible ICER was highly uncertain but likely to be substantially above the range NICE considers an acceptable use of NHS resources" whilst also saying that the ICER range was too uncertain to be useful did not make sense or "stack up". The panel noted that, during the hearing, the committee gave a range of ICERs based on a range of RTT rates that they described as "plausible", albeit that this range was wide. The panel concluded that the committee had an ICER range in mind when they concluded that any plausible ICER was likely to be above the threshold for cost-effectiveness. The panel therefore judged that the decision that there was too much uncertainty to assess the cost-effectiveness of voxelotor or to provide an ICER range was unreasonable.

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

Pfizer appeal point 2.2: The committee misunderstood the relationship between the proposed positioning/NHS population and the trial population. It drew incorrect conclusions.

157. Dr Oliver Shastri, for Pfizer, said that the committee were concerned by a mismatch between the population in the trial, the model and those eligible for voxelotor in the UK. The FDG and EAG report indicated this was a key area of uncertainty. Pfizer consider this misplaced. In the HOPE trial two thirds of patients were already receiving hydroxycarbamide so voxelotor should be considered a second line treatment for the majority of patients. He expected the majority, if not all, patients will be offered hydroxycarbamide and it is reasonable to consider RTT for those for whom hydroxycarbamide is not suitable. He explained that RTT is an option for patients, was included as a comparator in the scoping document and is reflected in Pfizer's model. He said that the committee's misunderstanding was apparent when it asked why RTT was excluded from the trial when the aim of the trial was to compare voxelotor against a placebo not against regular transfusion. This was because RTT increases haemoglobin so it would not have made sense to include patients on RTT in the trial as this would have rendered the results meaningless. He said that excluding RTT does not mean that the HOPE trial tells us nothing useful. The effectiveness of RTT is well established in clinical practice. Pfizer performed a naïve comparison as a pragmatic approach to evidence generation in a challenging disease area.

158. Professor Mark Layton, for Pfizer, said by way of background that hydroxycarbamide has been in use, based on a pivotal randomised controlled trial, since the mid-1990s and there is now 20 years of evidence on long term outcomes so it would be difficult for a new treatment to displace hydroxycarbamide. Thus a second line position for voxelotor is reasonable. He referred to the testimonies regarding the burden of RTT and patients who cannot receive

hydroxycarbamide and said that for these patients the landscape has been bleak. He said voxelotor is seen as a second line therapy for those who get an inadequate response from hydroxycarbamide or for whom it is ineffective.

159. In response to a question from the appeal panel, Professor Mark Layton said the population in the HOPE trial was very close to normal NHS practice, except that there were more patients in the HOPE trial (around two thirds) on hydroxycarbamide than in his clinical practice (around 20-40%).

160. Giles Monnickendam, for NICE, explained that the issue for the EAG and committee was not about where the clinicians were suggesting voxelotor would best be placed in NHS pathway but the difference between where Pfizer and committee were saying it should be placed on the pathway and the evidence from the HOPE trial. He said Pfizer acknowledged the mismatch between the trial population and its proposed positioning early on in the appraisal. He referred to page 2 of Pfizer Decision Problem Form which confirms the population in the trial did not exclusively include second line patients on hydroxycarbamide but relates to a broader population. So the trial relates to a broader population than Pfizer's submission population.

161. Giles Monnickendam said that during the decision problem meeting NICE advised Pfizer to submit both the population for which it had evidence and their proposed optimised population. He said Pfizer chose not to complete a submission for the full population.

162. Giles Monnickendam confirmed that the committee did understand Pfizer's positioning. He noted there was a change to that population after disquiet from using the word "unwilling" and Pfizer adjusted its position of "second-line treatment after hydroxycarbamide in people who are ineligible or intolerant, or for whom hydroxycarbamide alone

is insufficiently effective". Giles Monnickendam said the committee understood that but concluded there remained important differences between the trial population and Pfizer's positioning.

163. Giles Monnickendam said that the main issue in the modelling was the comparison with patients receiving RTT. He explained that the committee took the same approach to the HOPE trial data as it would for any clinical trial evidence: the committee considered the inclusion criteria, baseline characteristics of patients and the sickle cell therapies included in the control arm of the HOPE trial to conclude to what population the trial applied. The committee concluded that HOPE involved use of voxelotor as an add-on therapy for a young patient population early on in the pathway who had well controlled sickle cell disease and most importantly were not at a point in the pathway where RTT would be considered as the standard of care. Ineligibility, intolerance or inadequate response to hydroxycarbamide was not an inclusion criterion. 37% of patients were not on hydroxycarbamide at baseline and hydroxycarbamide is generally tolerated well in young patients. Pfizer gave no evidence to quantify the number of patients who had previously received hydroxycarbamide or who could be ineligible. Of the remaining 63% of patients on hydroxycarbamide at baseline the trial protocol specified that they were receiving a stable dose 3 months prior to the trial. So the committee considered these patients were well settled on hydroxycarbamide. Giles Monnickendam said that Pfizer produced no evidence of the number of patients that were considered to be inadequately controlled. He said the baseline characteristics meant more than 92% of patients had a haemoglobin of > 7 g/dL and that this was hitting the top end of the range of eligibility. He also noted that 90% of patients had no acute chest syndrome at baseline.

164. Giles Monnickendam said that the most important point was that RTT was not an option in either arm of the HOPE trial. The trial protocol stated that when agreeing to placebo treatment patients are not placed at any increased risk because no standard of care therapies will be withheld as a result. He said that this suggests patients for whom RTT could be considered as standard of care would not be included in the trial. He said that at ACM2 Pfizer made extensive arguments as to why the patients in the HOPE trial were at a decision point where they would be considered for RTT. However, he had not seen any evidence to support that position. HOPE was the pivotal trial for the marketing authorisation which was for a broader patient group. On balance the committee concluded that there was insufficient evidence to support the claim that a substantial proportion of patients in the HOPE trial were ineligible, intolerant or had an inadequate response to hydroxycarbamide.

165. Professor Mark Layton said that 2% of patients in HOPE per year had a crisis and this was quite representative of the population. He said crises are the tip of the iceberg. Professor Layton confirmed that it is his view that the HOPE trial was representative of real-world experience. He said he had never known a patient want to participate in a trial if their disease was under control, as the incentive to participate is the potential to benefit from a new agent. He said that two thirds of the HOPE participants were on hydroxycarbamide and still experiencing crises, which by definition is not a well-controlled population.

166. In response to questioning from the appeal panel, Giles Monnickendam said he did not consider the committee was expecting too much or was unreasonable in its requirements. He explained that the committee spent a lot of time reviewing these issues and discussing them with clinical experts to try to understand what criteria

they would apply in real world practice to determine eligibility for RTT. He noted the burden of RTT. He explained that the committee explored with experts to try to identify a set of patients from the trial who would have been eligible for RTT. As RTT was not permitted in the trial, it was odd the committee was being told trial patients were eligible for RTT, especially in light of the protocol, because if a patient was eligible and needed RTT it would be unusual for them to enter a trial where this was not an option. He explained the trial protocol said standard of care therapies would not be withheld but RTT was withheld in the trial, so the committee's interpretation was that RTT cannot have been considered as standard of care for this group of patients.

167. Giles Monnickendam said that in previous appraisals where there is a case for cost effectiveness in a subgroup the committee will look to understand the relevant evidence for that subgroup. Pfizer had the option to explore data for the subgroup but instead told the committee that all patients in the HOPE trial were at a place in the pathway where it could be considered that RTT was standard of care for all of them. This is where Pfizer and the committee disagree.

168. Giles Monnickendam said the committee acknowledged that the trial demonstrated a result in a certain patient population, but the question was whether this effect could be applied to the patient group identified by Pfizer model. He accepted that committees regularly face issues like this but typically there would be a subgroup and the effect would be recalculated for that group or it would be demonstrated there was no difference in effect in that subgroup so NICE can use the broader population results if concerned about statistical power based on subgroup results. That was not done here, and the committee can only consider what it is given. He did not know if this was because Pfizer had inadequate information to suggest a subgroup.

169. In response to a question from the appeal panel as to whether Pfizer recognise the concerns raised by Giles Monnickendam, Lucy Richardson, for Pfizer, said she considered these concerns to be incorrect. Lucy Richardson said that Pfizer's modelling does not assume all patients in HOPE will go on to RTT but rather that only a small proportion would be in scope for RTT as a comparator.

170. In response to a question from the appeal panel as to whether Pfizer understood the committee's concern the trial data did not reflect the population for whom voxelotor would be prescribed in NHS practice, Dr Oliver Shastri said the modelling was a conservative estimate of the proportion of patients for whom RTT would be appropriate. Pfizer model assumes [redacted] may be eligible for RTT. If more are eligible that is a good thing as it will save the NHS money.

171. Emma Clifton-Brown, for Pfizer, said that her understanding of the committee's concern was that because patients in the trial could not have RTT they must be a different type of patient. If that was the committee's view, Emma Clifton-Brown questioned why it had repeatedly asked for analyses that looked at equal levels of RTT in the two arms rather than excluding RTT altogether as their preferred assumption.

172. Giles Monnickendam said that this and the reasons for the scenarios considered by the committee will be explored under appeal point 2.3. He said that the committee focused on patients on RTT and whether HOPE was representative of them. That was because voxelotor at the price proposed by Pfizer was only cost effective when used for patients who would otherwise be on RTT. To the extent it would be given to patients who would not have had RTT, it would remain cost effective because of a halo effect. It was this group, and the cost saving of avoiding RTT, that drives the whole model. If voxelotor does not work for this group the ICER goes “through the roof”.

173. Emma Clifton-Brown said that commenting on the effect on the ICER speaks to Pfizer's concern that the committee had ICERs in mind that were not provided to Pfizer.

174. In response to a request for clarification, it was confirmed that the model was not based on patients being on both voxelotor and RTT but rather that the key issue was whether treatment with voxelotor would prevent the need for regular transfusions.

175. The appeal panel concluded as follows.

176. At the hearing, the appellants and committee agreed that concerns about the proposed positioning of voxelotor had been a key issue in this appraisal. This was of central importance to the negative decision because the committee were uncertain about the efficacy of voxelotor in the proposed population and because of the impact of the positioning on RTT rate, which was a key driver of the ICER (see Pfizer appeal point 2.3).

177. The panel agreed that both Pfizer and the EAG had explained their respective positions clearly and justified their arguments in a logical way (even though there was a fundamental disagreement between them). In this context, the panel judged that clinical expert opinion was of particular importance in helping to understand the wider context and allowing the committee to judge which view to prefer. The panel noted that patient and clinical expert feedback in the slides from ACM1 included a comment that the “positioning of voxelotor is clear and makes clinical sense”. The panel heard from clinical experts at the hearing. These experts did not agree with the committee’s analysis that the patients in HOPE were generally very well-controlled and at an earlier stage of the treatment pathway. They felt that patients would not have taken part in a trial if their disease had been adequately controlled, and the trial included patients who

would otherwise have been eligible for RTT. The clinical experts also said that hydroxycarbamide is the standard first-line treatment in NHS practice, and indeed, the high proportion of patients receiving hydroxycarbamide was itself an indication that this was not a low risk population. Overall, the panel concluded that the view from clinical experts throughout the appraisal was that Pfizer's proposed positioning of voxelotor was appropriate in reflecting likely clinical practice.

178. The panel were aware that it is particularly difficult to generate evidence in sickle cell disease, noted the health inequalities faced by this patient group, and considered that these matters needed to be taken into account when considering the evidence.

179. The panel did not think it was unreasonable for the committee to consider concerns about the positioning of voxelotor in decision-making and agreed that these concerns increased uncertainty. However, the panel agreed that the committee's concerns about the positioning of voxelotor had been one of the key drivers of the committee's decision that it could not provide an ICER range and led directly to the committee's conclusion that "any plausible ICER was highly uncertain but likely to be substantially above the range NICE considers an acceptable use of NHS resources". Taking together the clinical expert views with the need for particular flexibility in this appraisal, the panel judged that it was unreasonable, in light of the evidence provided to it, for the committee to have placed such substantial weight on its concerns regarding Pfizer's proposed positioning.

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

181. The panel noted it would expect NICE to reconsider the degree of weight it placed on concerns about the positioning of voxelotor.

Pfizer appeal point 2.3: To the extent that the committee considered that the rates of RTT modelled in the voxelotor and SoC arms of the model could be the same, and relied in the FDG on that being a possibility, it was unreasonable to do so.

182. Lucy Richardson, for Pfizer, explained that within the economic model there is a treatment mix which includes a world with and without voxelotor and considers RTT, hydroxycarbamide and a combination. In the absence of a clinical trial Pfizer did a robust Delphi panel exercise to demonstrate how the proportions would differ in a world with and without voxelotor. Lucy Richardson referenced slide 28 of the ACM2 slides, which explains the key differences in the rates of RTT in the voxelotor arm and notes that there was only a small proportion of patients on both voxelotor and RTT, compared with the standard of care (SoC) arm. She explained that both voxelotor and RTT are intended to raise haemoglobin levels so voxelotor can be seen as an alternative to RTT. She stated that it is scientifically and clinically implausible to have the same RTT rates in both the voxelotor and standard of care arms and it was illogical to consider this in the decision making.

183. Lucy Richardson stated that ahead of ACM2 Pfizer provided additional evidence regarding a world without voxelotor, which included market research, a de novo clinician survey, HES database and real-world data modified from the Delphi panel. The EAG concluded the RTT rate in the standard of care arm was reasonable. Lucy Richardson explained that Pfizer was unable to conduct further analysis on the proportion of RTT in the data as the registry data and Early Access to Medicines Scheme did not define transfusions. However, the ACM2 slides confirmed a combination of voxelotor and RTT would not be appropriate. She said if the committee was willing to accept the Delphi panel rates for the standard of care arm there

was no reason, in principle, why it should not accept the RTT rate in the voxelotor arm as they were both derived from same robust methodology. This was an ongoing fundamental misunderstanding despite Pfizer's attempts to provide clarifications and clinical input. Lucy Richardson stated the EAG still believed it was appropriate to run clinically implausible scenarios by equalising the RTT rates in the standard of care and voxelotor arms. This misunderstanding is highlighted in the FDG which states the EAG's exploratory estimates were substantially above the range that NICE considers an acceptable use of NHS resources when modelling RTT scenarios.

184. Professor Mark Layton, for Pfizer, said that it was self-evident that if a drug increases haemoglobin it will reduce the transfusion rate. He said that there was evidence voxelotor increases haemoglobin and the transfusion rate had been reduced to below 50% in those who received voxelotor. He said there was every reason to be confident that transfusion rates would reduce in patients receiving voxelotor. He explained that hydroxycarbamide also increases haemoglobin levels and that in a sense there are three treatment options for patients with the common effect of increasing haemoglobin levels. Of those three RTT is the most burdensome and carries its own risks.

185. In response to a question from the appeal panel as to whether it was scientifically and clinically implausible for the same rates to be applied to both arms, Dr Megan John, for NICE, said the last comment from Professor Mark Layton regarding hydroxycarbamide demonstrated why this is so challenging: the committee did accept voxelotor increases haemoglobin at 28 weeks, but the committee was not sure if this went far enough to accept the conclusions from the trial as plausible.

186. Giles Monnickendam, for NICE, took the panel through the scenario analyses. He explained the committee was not trying to do anything

that was clinically implausible, unreasonable or irrational. He explained that it is the gap between the rates of RTT in the two arms that matters and a small percentage change in that gap can have a big impact on the ICER. When using Pfizer's RTT rates the ICER was below the figure normally accepted as acceptable, but when the RTT rates were set equal it was very substantially higher. Pfizer's base case had an important gap between the two: [redacted] in the voxelotor arm and around [redacted] in the standard of care arm. Even with the RTT rate for voxelotor set to half that for the standard of care arm the ICER was "well above the normal cost effectiveness threshold".

187. Giles Monnickendam explained that the scenario analysis considering equal rates had three objectives. First, to demonstrate the importance of the assumptions and the impact of the rates. Secondly, as an attempt to estimate the ICER in a scenario where voxelotor was not positioned as an alternative to RTT, which the committee thought was in line with the clinical evidence from HOPE. Thirdly, to consider the ICER if voxelotor was used as an alternative to RTT but was not in fact effective in reducing the need for RTT.

188. Giles Monnickendam said it was clear from the EAG report that the EAG disagreed fundamentally with Pfizer on whether voxelotor could be an alternative for RTT. The EAG's view was based on the lack of supporting clinical evidence, that the HOPE trial did not compare voxelotor and RTT, that there were no indirect treatment comparisons, that it was not the appropriate population and that there was no robust evidence on efficacy of the comparator (RTT). The EAG proposed that RTT was removed from the model or both arms were modelled with equal rates to reflect that RTT was not an alternative. This was effectively modelled in the first scenario ([redacted] for both arms). Giles Monnickendam explained that by ACM2 the

committee wanted to consider further scenarios. He said Pfizer model did not include subsequent therapies, so the EAG were asked to produce a scenario with a similar figure in both arms. He explained this did not assume that patients will have voxelotor in combination with RTT. Rather it assumes that voxelotor at baseline is 100% ineffective in avoiding the need for RTT so the same proportion of patients will go on to receive RTT as they would in the world without voxelotor. The committee did not conclude this was what would happen but wanted to understand the modelling. He confirmed the committee understood that using equal rates of RTT in both arms represented ineffective displacement of RTT by voxelotor, rather than voxelotor being initiated with RTT.

189. In response to questions from the appeal panel as to the committee's decision to model equal rates as a worst-case scenario and the committee's view on the Delphi data on the difference between the rates for the two arms, Giles Monnickendam confirmed that the committee considered the Delphi panel data. The committee understood that clinicians were asked to confirm what proportion of patients would be on RTT if voxelotor did not exist. The committee took the view at ACM1, and was supported by evidence at ACM2, that this question was asked in an appropriate way so the committee could rely on this evidence for the standard of care arm. However, when the committee looked at the questions for the voxelotor arm these did not appear to ask clinicians for a view, based on data presented to them, on what number of patients on voxelotor would have the same short term or long-term efficacy as they would have had on RTT, such that they could be switched from RTT to voxelotor with no health detriment (i.e. a best practice question trying to understand the substitutability of voxelotor for RTT). Giles Monnickendam also noted that the Delphi report said clinicians struggled with the hypothetical

scenario to give accurate responses. He considered this to suggest the clinicians did not understand what they were being asked to do.

190. Lucy Richardson said Pfizer followed the right procedures for the Delphi panel. In the first round the clinicians did not come to an overall consensus. However, when they spoke to each other they agreed that [redacted] was appropriate for the voxelotor arm. Lucy Richardson said this was a robust methodology. She said that Pfizer never suggested patients should switch from RTT to voxelotor, but that voxelotor could be an alternative treatment before patients start RTT.

191. Dr Megan John said that the suggestion that Pfizer's positioning of voxelotor was before RTT was different from what Pfizer had submitted.

192. Lucy Richardson said the model did not assume voxelotor would displace 100% of those patients already on RTT but that there is an earlier decision point at which a choice is made between RTT or voxelotor.

193. Dr Oliver Shastri, for Pfizer, referred the appeal panel to a decision tree in Pfizer's consultation response regarding Pfizer's position ("Figure 1. Comparison of the HOPE trial population and modelled population in the “world with” and “world without” voxelotor scenario").

In response to a question from the appeal panel as to how in the voxelotor arm Pfizer selected [redacted] Lucy Richardson confirmed this was selected by the clinicians as their agreed overall consensus.

194. Tinu Williamson-Taylor, for SCS, confirmed that she was not on RTT and went on to describe the benefits she experienced from voxelotor.

195. In response to questions from the appeal panel, Giles Monnickendam said HOPE was a correctly designed trial and appropriate for the broad patient population. He said the committee's concerns were based on more than the HOPE trial excluding patients on RTT. He said that if the committee had known a certain percentage of patients in the HOPE trial were eligible for RTT then the committee would still want to look at the effectiveness isolated in that subgroup because of Pfizer's positioning and importance of the subgroup to the modelling.

196. Professor Mark Layton acknowledged the critical importance of this group but said that any sickle cell patient eligible for disease modifying treatment will be considered for RTT. He explained that when he discusses treatment options with patients this will include hydroxycarbamide, RTT and a clinical trial, like HOPE, so by definition they are patients that would be eligible for RTT.

197. In response to a question from the appeal panel as to whether it might have been helpful to invite further discussion from clinical experts at ACM2 to try and resolve these differences, Dr Megan John said Pfizer is suggesting there was clinical consensus but the Delphi report provided views of clinical experts who had been asked questions in a specific way by Pfizer. Dr John said the EAG took the views of its own experts and saw a difference of opinion. Stakeholder responses to consultation also varied and Dr John said it would have been difficult to put increased weight on a small number of experts in the room over those other experts that had expressed views in the process.

198. Giles Monnickendam further explained that these were issues raised by the EAG and discussed already at ACM1, the committee had been provided with the Delphi panel report as evidence from Pfizer that voxelotor could effectively replace RTT and the committee had asked Pfizer to provide more evidence between ACM1 and ACM2 but chose

not to do so. Therefore there was nothing new at ACM2 and they were discussing the same issues that were apparent at ACM1, which had already been through consultation. Giles Monnickendam said he was unclear how this question could have been answered unless Pfizer produced data from a subgroup in the HOPE trial and explained how it might be possible to identify patients eligible for RTT, though he appreciated that there are not clear UK guidelines on when it is best for a patient to put them on RTT. If Pfizer had presented criteria and identified a subgroup from the trial or done an expert elicitation study on likely effectiveness of voxelotor substituting for RTT this could have been considered at ACM2, but these things were not done.

199. Lucy Richardson said Pfizer did submit new evidence to address uncertainty at ACM1 around RTT rates for the standard of care arm. Pfizer provided new HES CPRD data, market research and a whole new clinical study including a clinical survey.

200. Dr Oliver Shastri noted Pfizer's appeal letter contains a table that summarises this position.

201. Professor Mark Layton clarified that there are guidelines on RTT which broadly overlap with hydroxycarbamide and guidance for alternative treatments for similar clinical scenarios which he would expect would be the same for voxelotor.

202. In response to a question from the appeal panel regarding whether it would have been helpful for clinicians to comment on the 2a, 2b and 2c scenarios created for ACM2, Giles Monnickendam explained that the committee is very careful about what is presented to clinicians and what they are being asked to validate. He said the committee asks questions to clinicians in respect of their direct experience rather than asking them to guess. He explained that from the evidence the

committee identified two ends of a range with any point on that range being equally plausible. The committee considered it would be inappropriate to ask the clinicians to identify a single point over any other in this range as this would be based on a guess.

203. John James, for SCS, said that this conversation helps illustrate why further discussions would have been appropriate and NICE's desire to seek perfection. He said the nature of sickle cell disease means perfection is not appropriate or comparable to seeking perfection when appraising drugs for other diseases. He said that this conversation should have been held and issues resolved earlier and there must be flexibilities when dealing with a condition like this.

204. Linda Landells, for NICE, clarified that the reference to the 2a, 2b and 2c scenarios came from clinical expert opinion (the Delphi panel) and this was taken into account when they were generated.

205. The appeal panel concluded as follows.

206. At the hearing, the appellants and committee agreed that the difference in RTT rate between the voxelotor and standard of care groups was the main driver of the ICER. There was agreement that there was no direct trial evidence to inform the rates of RTT in the model. The panel accepted the argument made by the committee, that it is *possible* that voxelotor is not effective in avoiding RTT in those who would otherwise need it. The panel also accepted Pfizer's argument, supported by expert opinion from a Delphi panel, that it is *likely* that voxelotor will reduce the need for RTT because it increases haemoglobin (an effect which the committee acknowledged).

207. The panel were aware that the committee had modelled a scenario with equal rates of RTT in the voxelotor and standard of care arms as one of a range of scenarios. It accepted the primary purpose of this

scenario analysis had been to explore the importance of different assumptions in the model. The panel noted that the committee had been aware that voxelotor and RTT would not be used together: because subsequent lines of therapy were not included in the model, adjusting the baseline RTT rate in the voxelotor arm was the only way to explore a scenario in which voxelotor was inadequate and patients switched to RTT.

208. The panel did not accept Pfizer's argument that, having accepted the RTT rate for the standard of care arm in the Delphi study, the committee were also obliged to accept the RTT rate for voxelotor from this study. They agreed with the committee's view that expert estimates of the former were based on greater experience and more likely to be reliable, and also noted the committee's concern about the way in which the question about RTT in the voxelotor arm had been asked.

209. The panel accepted that the committee had not expressed a preference for the scenario in which RTT rates were the same for voxelotor and standard of care, but rather had considered this as one of a range of possible scenarios. The panel did not find this unreasonable. The panel judged that the negative recommendation did not result from the ICER from this particular scenario being given unreasonable weight, but rather from a combination of the committee's view on uncertainty and the fact that ICERs were above the usual range in all the scenarios that the committee considered plausible.

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

Conclusion and effect of the appeal panel's decision

211. The appeal panel therefore upholds the appeal by Pfizer on its appeal points 1a.1, 1a.2, 1b.1, 2.1 and 2.2 and upholds the appeal by SCS on its appeal point 1b.1. The appeal is dismissed on all other grounds.

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

    a. The appraisal committee should provide the ICERs or an ICER range that informed decision-making and invite stakeholder comment on these and on the scenario analyses discussed at Pfizer's appeal point 1a.2, so that the committee can consider those observations and whether the guidance should be revised as a result. One way to achieve this would be a further round of consultation.

    b. The committee should consider whether there are additional steps it could take to make reasonable adjustments for the substantial disadvantage identified for people with sickle disease. This might include providing a range of ICERs that informed decision-making.

    c. The committee should reconsider the degree of weight it placed on concerns about the positioning of voxelotor.

213. 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.

INTRODUCTION

To inform the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) of the clinical and cost effectiveness of voxelotor for treating haemolytic anaemia in people with sickle cell disease, NICE has asked the External Assessment Group (EAG) to provide cost effectiveness results for the following scenarios to inform NICE Appraisal Committee decisions:

- Scenario 2a: company base case with no direct utility increase associated with an increase of 1g/dL in Hb
- Scenario 2b: company base case with 0.028 utility increase associated with an increase of 1g/dL in Hb
- Scenario 2c: company base case with 0.075 utility increase associated with an increase of 1g/dL in Hb
- Scenario 2d: company base case with 0.109 utility increase associated with an increase of 1g/dL in Hb
- Scenario 3a: company base case with RTT rate for voxelotor set to [redacted]%
- Scenario 3b: company base case with RTT rate for voxelotor set to [redacted]%
- Scenario 3c: company base case with RTT rate for voxelotor set to [redacted]%

This appendix contains cost effectiveness scenario results using the Patient Access Scheme price for voxelotor and list prices for epoeitin alfa, epoeitin beta and darbepoetin alpha. The company base case results have been generated using 50,000 individual patient iterations. However, as the ICER per QALY gained converges at 5,000 iterations and the significant length of time it takes to run the company model, the generated cost effectiveness results use 10,000 iterations.

COST EFFECTIVENESS RESULTS

Table 1 Scenario 2a: Company base case with no direct utility increase associated with an increase of 1g/dL in Hb (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hb=haemoglobin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SoC=standard of care

Table 2 Scenario 2b: Company base case with 0.028 utility increase associated with an increase of 1g/dL in Hb base case results (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hb=haemoglobin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SoC=standard of care

Table 3 Scenario 2c: Company base case with 0.075 utility increase associated with an increase of 1g/dL in Hb base case results (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hb=haemoglobin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SoC=standard of care

Table 4 Scenario 2d: Company base case with 0.109 utility increase associated with an increase of 1g/dL in Hb base case results (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CMU=Commercial Medicines Unit; Hb=haemoglobin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SoC=standard of care

Table 5 Scenario 3a: Company base case with RTT rate for voxelotor set to [redacted]% (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; RTT=regular transfusion therapy; SoC=standard of care

Table 6 Scenario 3b: Company base case with RTT rate for voxelotor set to [redacted]% (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; RTT=regular transfusion therapy; SoC=standard of care

Table 7 Scenario 3c: Company base case with RTT rate for voxelotor set to [redacted]% (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; RTT=regular transfusion therapy; SoC=standard of care