NICE National Institute for Health and Care Excellence

NICE guidance

Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria

Technology appraisal guidance
Published: 23 October 2024

www.nice.org.uk/guidance/ta1010

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Danicopan is recommended, as an add-on to ravulizumab or eculizumab as an option for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults who have residual haemolytic anaemia, only if:

- they have clinically significant extravascular haemolysis while on treatment with a complement component 5 inhibitor (C5 inhibitor) and
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with danicopan 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 healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Standard care for PNH with haemolytic anaemia includes the C5 inhibitors ravulizumab and eculizumab. After a C5 inhibitor, people who still have anaemia (residual haemolytic anaemia) and symptoms of PNH usually have pegcetacoplan. For this evaluation, the company asked for danicopan as an add-on to ravulizumab or eculizumab to be considered only for PNH in adults who have clinically significant extravascular haemolysis. This does not include everyone who it is licensed for.

Evidence from clinical trials shows that danicopan with a C5 inhibitor increases haemoglobin levels and reduces the need for blood transfusions more than a C5 inhibitor alone. There is no direct evidence comparing danicopan with pegcetacoplan and the results from an indirect comparison are uncertain.

The economic evidence for danicopan add-on treatment has some uncertainties, including long-term breakthrough haemolysis rates and around some of the assumptions used to estimate cost effectiveness. But, the most likely cost-effectiveness estimates are within the range usually considered a cost-effective use of NHS resources. So, danicopan is recommended.

2 Information about danicopan

Marketing authorisation indication

2.1 Danicopan (Voydeya, Alexion) is indicated as 'an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of danicopan is £1,369.80 for a 90-tablet bottle of 50-mg tablets and £2,739.60 for a 90-tablet bottle of 100-mg tablets (company submission).

2.4 The company has a commercial arrangement. This makes danicopan available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Alexion, 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 the condition

3.1 Paroxysmal nocturnal haemoglobinuria (PNH) is a rare blood condition caused by an acquired mutation of the PIG-A gene within bone marrow stem cells. PNH results in the body's immune system attacking its red blood cells. The breakdown of red blood cells can happen within the blood vessels (intravascular haemolysis) or outside the blood vessels (extravascular haemolysis). This often causes anaemia, which is treated with blood transfusions, and causes symptoms of haemolysis and thrombosis. Because PNH is a chronic condition, the symptoms continue for a long time. The patient experts stated that symptoms affect people in different ways. Symptoms can include:

- abdominal pain
- kidney problems
- fatigue
- shortness of breath
- bleeding
- blood clots
- difficulty swallowing, and
- organ damage.

The patient experts added that acute events like food poisoning or chest

infections can trigger acute haemolysis. This can cause new or worsening symptoms of intravascular haemolysis. The committee concluded that PNH can substantially affect health-related quality of life.

Treatment pathway and proposed positioning

3.2 Standard care for newly diagnosed PNH is intravenous treatment with a complement component 5 (C5) inhibitor. Specifically, either eculizumab every 2 weeks or ravulizumab every 8 weeks, in line with NICE's technology appraisal guidance on ravulizumab. The clinical experts explained that ravulizumab is the preferred treatment option, except during pregnancy. Eculizumab is used during pregnancy because its side-effect profile is more established. The clinical experts added that a small number of people may choose to have eculizumab. If there is residual anaemia after treatment, people can either stay on the same C5 inhibitor, or switch to an alternative C5 inhibitor or to pegcetacoplan. This is in line with NICE's technology appraisal guidance on pegcetacoplan (referred to from here as TA778). Pegcetacoplan is a complement component 3 (C3) inhibitor administered by subcutaneous injection twice per week. The clinical experts explained that the treatment choice for residual anaemia is dependent on the cause and extent of the symptoms (particularly whether people need transfusions). For example, residual anaemia may be caused by intravascular haemolysis, which would usually be treated by optimising the dose of C5 inhibitor. Whereas for people whose symptoms are caused by extravascular haemolysis and who need regular transfusions, switching to pegcetacoplan may be more appropriate. The clinical experts explained that about 80% of people with PNH having C5 inhibitors will remain anaemic. Of these, about 30% of people will have clinically significant extravascular haemolysis. For this appraisal the company asked for danicopan as an add-on to eculizumab or ravulizumab to be considered only for adults with PNH who have clinically significant extravascular haemolysis. The company stated that there is no standardised definition of clinically significant extravascular haemolysis in UK clinical practice. The EAG considered that this could lead to subjectivity in the eligibility for danicopan add-on therapy in routine NHS use. A clinical expert explained that to diagnose clinically significant extravascular haemolysis, haemoglobin levels and absolute reticulocyte count would be considered alongside other clinical parameters and symptoms as part of a wider clinical picture. Non-haematological causes would also be excluded,

potential intravascular haemolysis would be assessed and C3 loading on PNH red blood cells would be checked. They added that in the NHS, the PNH service is well established and that clinical management is consistent between the 2 NHS PNH centres. The diagnosis of people with clinically significant extravascular haemolysis and their eligibility to have danicopan add-on therapy would be discussed at monthly multidisciplinary meetings. The committee concluded that the company's proposed positioning of danicopan add-on therapy for PNH in adults with clinically significant extravascular haemolysis is appropriate.

Comparators

3.3 Based on the company's proposed positioning of danicopan add-on therapy, the only comparator included in the company submission was pegcetacoplan. The company stated that extravascular haemolysis only becomes clinically significant after treatment with a C5 inhibitor and neither ravulizumab or eculizumab addresses extravascular haemolysis. It added that pegcetacoplan is the only treatment recommended by NICE for clinically significant extravascular haemolysis and is considered standard care for the condition in the UK. So, the company considered pegcetacoplan to be the only relevant comparator and not the C5 inhibitors. The EAG considered that current standard care for clinically significant extravascular haemolysis includes remaining on a C5 inhibitor. So it considered eculizumab and ravulizumab could not be excluded as comparators. It added that comparing danicopan add-on therapy with C5 inhibitors alone is more robust than a comparison with pegcetacoplan. This is because there are fewer concerns about the comparability of the 2 arms in the ALPHA trial, which is the primary source of the clinical-effectiveness evidence (see section 3.4). This is because of the limitations with the naive comparison and the indirect treatment comparison (see section 3.5). The EAG did an analysis, comparing danicopan add-on therapy with C5 inhibitors alone using the results from the ALPHA trial. The clinical experts stated that for clinically significant extravascular haemolysis, they would usually prescribe a proximal inhibitor. They added that pegcetacoplan is currently the only routinely commissioned proximal inhibitor available in NHS clinical practice. But a small proportion of people with clinically significant extravascular haemolysis may not switch because of personal preference (for example, because they do not want to self-administer pegcetacoplan). But, the clinical experts agreed with the company that staying on a C5 inhibitor would not

address clinically significant extravascular haemolysis and that pegcetacoplan is the only relevant comparator. The committee considered that proximal inhibitors are the preferred treatment option for clinically significant extravascular haemolysis. So, the committee concluded that pegcetacoplan is the appropriate comparator.

Clinical effectiveness

ALPHA trial

3.4 The primary clinical-effectiveness evidence for danicopan came from the ALPHA trial, which was a phase 3, multinational study. It consisted of a 12-week, double-blind, randomised-controlled period, during which danicopan plus eculizumab or ravulizumab (n=57) was compared with placebo plus eculizumab or ravulizumab (n=29). The 12-week randomised-controlled period is referred to as treatment period 1. The trial included adults with PNH having eculizumab or ravulizumab who had a haemoglobin level of 9.5 g/dl or less with an absolute reticulocyte count of 120 × 10^9/litre or more. Treatment period 1 was followed by a 12-week open-label treatment period in which everyone having placebo switched to danicopan. This is referred to as treatment period 2. This was followed by an ongoing open-label extension period of up to 2 years. The primary efficacy endpoint in the ALPHA trial was change in haemoglobin level from baseline at week 12. In its submission, the company presented efficacy results based on the interim efficacy analysis set. This was defined as the first 75% of people (n=63) out of the total planned enrolment of the trial (n=84) who had completed treatment period 1. Based on the first interim analysis set (IA1), the least squares mean change in haemoglobin from baseline to week 12 was calculated. In the danicopan arm the change was 2.94 g/dl. In the placebo arm it was 0.50 g/dl. This resulted in a difference of 2.44 g/dl between the treatment arms when adjusting for stratification factors ($p<0.0001$). Also at week 12, based on IA1, 83.3% of people in the danicopan arm did not have a transfusion, compared with 38.1% of people in the placebo arm. This resulted in a difference of 41.7% between the treatment arms when adjusting for stratification factors ($p=0.0004$). A second interim analysis (IA2) was repeated when the 63 people from IA1 completed treatment period 2. Based on IA2, for people who had danicopan in

both treatment period 1 and treatment period 2 (n=41), the least squares mean change in haemoglobin from baseline was 3.17 g/dl. In the same group, 78% of people did not have a transfusion between week 12 and week 24. The results from a third interim analysis (IA3), in which more people had completed treatment period 1 and treatment period 2, were presented by the company after its submission. But these results are considered confidential by the company so cannot be reported here. The committee concluded that danicopan add-on therapy was clinically effective compared with C5 inhibitor monotherapy for people with residual anaemia after treatment with a C5 inhibitor.

Indirect treatment comparison

3.5 Because there was no direct evidence comparing danicopan add-on therapy with pegcetacoplan, the company did a series of matching-adjusted indirect treatment comparisons (MAICs). The company used data from the ALPHA trial for danicopan add-on therapy. For pegcetacoplan, it used data from the PEGASUS trial, a phase 3, open-label, randomised-controlled trial. It compared pegcetacoplan (n=41) with eculizumab (n=39) in adults with PNH whose haemoglobin levels were 10.5 g/dl or below despite treatment with eculizumab. Before adjusting for treatment-effect modifiers or prognostic-factor variables, the company used part of the population from the ALPHA trial to align more closely with the PEGASUS trial population. This was based on body mass index and platelet count. The company selected mean baseline haemoglobin level and mean baseline reticulocyte count as the covariates for the MAICs, based on clinical opinion and data availability. The effective sample sizes were also taken into account, which limited the number of covariates able to be adjusted for in the analyses. Unanchored and anchored MAICs were done for selected key outcomes at 12 weeks for danicopan add-on therapy and at 20 weeks (including 4-week run in period) for pegcetacoplan. The company noted that the reweighted ALPHA trial population differed in key treatment-effect modifiers or prognostic-factor variables from the PEGASUS trial population. For example, prior transfusion history and baseline bilirubin levels remained unbalanced between trial populations. Also, a small effective sample size after adjustment introduced further uncertainty. Both the company and EAG considered the MAIC results unsuitable for drawing conclusions on the relative efficacy between danicopan add-on therapy and pegcetacoplan. The committee agreed that the MAIC results

were not sufficiently robust for estimating the relative efficacy between danicopan add-on therapy and pegcetacoplan.

Economic model

Company's modelling approach

3.6 The company presented a de novo 4-state Markov cohort model with a lifetime time horizon of 45.7 years. This comprised health states defined by haemoglobin levels ('low haemoglobin' and 'moderate haemoglobin'), blood-transfusion status, and death. The health states are mutually exclusive and mutually exhaustive with a cut-off haemoglobin level of 9.5 g/dl. All people were assumed to enter the model in the low haemoglobin with no transfusion state and progress through the model in 4-week cycles. A key driver of cost effectiveness was breakthrough haemolysis (BTH) events, and the associated disutility and management costs (see section 3.9). The committee concluded that the company's model structure was appropriate for decision making.

Transition probabilities

3.7 Because of the limitations with the indirect treatment comparison (see section 3.5), the company derived transition probabilities for danicopan add-on therapy directly from the ALPHA trial. For the pegcetacoplan arm, the company used transition probabilities reported by Hakimi et al. (2022) in their published cost-effectiveness analysis based on the PEGASUS trial. Hakimi et al. used a different threshold to define haemoglobin health states (10.5 g/dl rather than 9.5 g/dl; see section 3.6). A company scenario analysis showed that this had a small impact on outcomes. The EAG noted that the company's choice of transition probabilities does not account for underlying differences in population baseline characteristics or in the models used to estimate the transition probabilities. The EAG considered that almost all the same limitations with the company's MAICs (see section 3.5) also applied to the naive comparison and that when comparing both ALPHA and MAIC populations, there are a number of important differences with the PEGASUS population. It also noted that the

danicopan add-on therapy transition probabilities were derived from the IA2 data-cut, despite a later data-cut being available (see section 3.4). After the first committee meeting, the company updated its base case using transition probabilities from IA3, which was the latest available data-cut from the ALPHA trial. Overall, the EAG considered that the relative efficacy estimates were too uncertain to provide a reliable estimate of cost effectiveness. It presented a range of analyses assessing the impact of model parameters on cost-effectiveness estimates. It presented a scenario analysis assuming equal efficacy between danicopan add-on therapy and pegcetacoplan. The committee considered that it was not clear which was the most appropriate approach and that both methods were highly uncertain. It noted that assuming equal efficacy between danicopan add-on therapy and pegcetacoplan, compared with using the naive transition probabilities, only had a small impact on cost effectiveness. The committee concluded that it would use the naive transition probabilities as a basis for decision making, despite their limitations. It also concluded that it preferred transition probabilities for danicopan add-on therapy derived from the IA3 data-cut and that the lack of robust transition probabilities added uncertainty to the economic analysis.

Modelling of BTH probabilities

3.8 Because of the limitations associated with the indirect treatment comparison (see section 3.5), the company derived the per-cycle probabilities for BTH events for danicopan add-on therapy directly from the ALPHA trial. It was assumed that the BTH-event probabilities for week 52 onwards were equal to the observed rate in the ALPHA trial between weeks 25 and 52 (long-term extension period). In the ALPHA trial not all BTH events needed intervention. So, the company based the rates only on events that were classified as needing an intervention. For the pegcetacoplan arm, the company based the per-cycle probabilities on the PEGASUS trial. The BTH-event probabilities for weeks 1 to 16 were equal to the observed BTH rate during the 16-week randomised-controlled trial period of the PEGASUS trial. In the company's original base case, the BTH-event probabilities for week 17 onwards were based on the BTH rate observed during the PEGASUS trial open-label extension (OLE; 29.68% annual rate). After the first committee meeting, the BTH-event probabilities for week 17 onwards were based on the BTH rate observed during a 48-week pegcetacoplan OLE study. This comprised

5 parent studies including PEGASUS (Patriquin et al. 2024). The company assumed that because all observed BTH events in PEGASUS resulted in dose escalation, all BTH events were included. It also had clinical expert input that the criteria used to classify a BTH event in the PEGASUS trial aligns with UK clinical practice. The company's modelling approach resulted in a higher BTH rate in the pegcetacoplan arm (28.37% annual rate for weeks 1 to 16 and 23.47% annual rate for week 17 onwards) compared with the danicopan add-on therapy arm (0% rate for weeks 1 to 24 and 3.07% annual rate for week 25 onwards). The EAG considered that it was unclear whether the thresholds for BTH interventions were the same across trials and whether the degree of any potential intervention was comparable. It also considered that a naive comparison of BTH rates was not robust because of the differences between trial populations (see section 3.5) and that it lacked face validity. The company said that there will be a lower likelihood of BTH events with danicopan add-on therapy than with pegcetacoplan because of the C5 inhibitor backbone. It added that a company clinical expert considered the modelled long-term BTH rate for pegcetacoplan to be reflective of the expected BTH rate for pegcetacoplan. The company also provided 2 studies, Griffin et al. (2024a) and Kulasekararaj et al. (2023), which showed higher BTH rates for pegcetacoplan compared with ravulizumab. In Griffin et al. (2024a), the annual BTH rate was 18.35% for pegcetacoplan, compared with an annual BTH rate of 1.69% in Kulasekararaj et al. (2023) for ravulizumab. It also stated that clinical experts noted that the PEGASUS trial recruited a more severely ill population than the Griffin et al. (2024a) study, which accounts for the slightly higher BTH rate observed in the PEGASUS trial. The EAG stated that the studies provided by the company did not address its concerns about the limitations of the naive comparison of BTH rates. It added that the studies may underestimate pegcetacoplan BTH rates because they generally report the number of people rather than the number of events. The company stated that it considered the modelling conservative in this regard because the total number of BTH events was likely higher than the number of people. The EAG noted that if pegcetacoplan dose escalation (see sections 3.9 and 3.10) was accurately modelled, then it would expect the BTH rate for pegcetacoplan to reduce over time (and potentially converge with BTH rates for danicopan add-on therapy over time). The EAG preferred to assume the long-term (week 25 onwards) BTH rate for pegcetacoplan was twice the long-term BTH rate used by the company for danicopan add-on therapy. That is, an annual rate of 6.06% for pegcetacoplan. It also provided a scenario analysis in which the long-term BTH rate for

pegcetacoplan was triple the long-term BTH rate used by the company for danicopan add-on therapy. That is, an annual rate of 8.97% for pegcetacoplan. It acknowledged that applying these BTH rates from 25 weeks may result in convergence of BTH rates sooner than expected in clinical practice. But it does not expect the difference in BTH rates between danicopan add-on therapy and pegcetacoplan to remain as high as modelled by the company for the length of the modelled time horizon. Especially considering that if pegcetacoplan dose escalations do not provide sufficient control then returning to C5 inhibitor monotherapy may be preferred. The clinical experts stated that they would expect people having danicopan add-on therapy to have lower BTH rates than people having pegcetacoplan. This is because they are also having a C5 inhibitor with danicopan, and because of the differences in the mechanism of action between C5 inhibitors and pegcetacoplan. The clinical experts also stated that they would expect the long-term annual BTH rates for pegcetacoplan to be higher than in the EAG preferred assumptions and scenario analysis (6.06% and 8.97% annually, respectively). A clinical expert added that the highest BTH rates would typically occur in the first year and the rate may reduce in the second year of treatment. They estimated that a long-term BTH rate of 10% to 20% may be plausible for pegcetacoplan. But, because of the lack of long-term data, this estimate is highly uncertain. The committee noted that the long-term BTH rates were a substantial driver of cost effectiveness. It also noted that the long-term BTH rates in the model were based on less than 2-years follow up and extrapolated for the remaining lifetime time horizon. It also considered that the BTH rate for pegcetacoplan may reduce over time because some people have permanent dose escalations. It also suggested that if the BTH rate remained high despite permanent dose escalations, then some people may switch to an alternative treatment. So, assuming that the BTH rate from Patriquin et al. (2024) would be maintained for the remaining modelled time horizon was very uncertain. It considered that the BTH rate for danicopan add-on therapy would be lower than that for pegcetacoplan. It considered the long-term rate for pegcetacoplan would be higher than the rates proposed by the EAG (6.06% to 8.97% annually) but lower than the company's base-case estimate (23.47% annually). The committee considered the range of annual BTH rates for pegcetacoplan from various sources. It concluded that, as a basis for pragmatic decision making, it preferred to assume a long-term BTH rate for pegcetacoplan of between 10% and 18% annually.

Modelling of costs associated with BTH

3.9 In the company's original base case, it was assumed that people having pegcetacoplan who experience a BTH event will increase their pegcetacoplan maintenance dose from twice weekly to:

- once every 3 days for the first dose escalation, and
- 3 times per week for the second dose escalation (in the event of a further BTH event).

Under these assumptions, most people in the pegcetacoplan arm eventually escalated to a maintenance dose of 3 times per week. The company stated that this dose-escalation regimen for BTH is in line with the approach adopted in an OLE study of pegcetacoplan. It was also confirmed by clinical experts to reflect NHS clinical practice. The summary of product characteristics for pegcetacoplan allows escalation beyond the 1,080 mg twice-weekly dose. The company also provided 2 references that it stated supported the use of pegcetacoplan 3-times weekly for BTH. The first was Griffin et al. (2024a), a real world-study summarising the management of BTH events in clinical practice for people having pegcetacoplan in the UK and France. The dosing regimen was not included for all people in the study. The EAG stated that 13 out of 48 people experienced BTH events in the study. Of those, 4 (30.8%) were escalated to have pegcetacoplan every 3 days, and 2 (15.4%) were escalated to have 3 doses per week. It considered that the others may have had temporary dosing changes but did not appear to have their regular dose adjusted. The company provided another study, Griffin et al. (2024b), based on a pegcetacoplan OLE study. It provided data about intensive pegcetacoplan dosing in the management of acute BTH events. The EAG stated that the pegcetacoplan OLE by Griffin et al. (2024b) focused on dose escalation of pegcetacoplan in cases of acute BTH. So, the population in the study is not representative of the target population of this appraisal. The EAG added that only 4 of the 13 higher dosing regimens were reported to be due to BTH events. It was also unclear whether other dose increases were sustained after the BTH event was under control. Overall, the EAG acknowledged that some escalation happens in clinical practice. But it stated that neither of these studies presents evidence of BTH events or management for periods close to the 45-year time horizon of the company's

economic model. And neither demonstrates dose escalation to the magnitude modelled by the company. The EAG added that the company's dose-escalation approach appears inconsistent with TA778, which assumed pegcetacoplan dosing would be fixed at 2 doses per week. A clinical expert stated that for people having pegcetacoplan, a BTH event requiring treatment would be treated either with a single dose of eculizumab or an increased dose of pegcetacoplan. The dose of pegcetacoplan would usually be reduced back to twice-weekly maintenance dosing after 2 to 3 months. For example, if a BTH event was caused by an infection, then it would not be clinically justified to maintain the increased pegcetacoplan dose beyond 2 to 3 months. They explained that there are some people who have recurrent severe episodes of BTH, and for these people, healthcare professionals would consider a combination of different medicines to control the BTH. They estimated that this is only the case for 2 or 3 people in the UK. The committee acknowledged that some people on pegcetacoplan who experience BTH would have their maintenance dose increased. But the committee considered that the evidence provided by the company and the clinical expert input did not support a maintained dose increase. It considered that it may be appropriate to assume some people having pegcetacoplan have a single dose of eculizumab to manage a BTH event, rather than a pegcetacoplan dose increase. But, there was uncertainty about the proportion of people who would have either treatment option. So, the committee requested data on the proportion of people having pegcetacoplan for whom a BTH event is treated with single dose eculizumab or by increasing the pegcetacoplan dose at the first committee meeting.

3.10 After the first committee meeting, the company acknowledged that a BTH event may happen because of an acute event such as an infection. This would usually be treated with a temporary dose escalation of pegcetacoplan. But for a BTH event, which may happen because of an insufficient level of complement inhibitor in a person's plasma, that person would stay on the escalated dose if there was no identifiable cause. Clinical experts consulted by the company estimated that approximately 50% of people having pegcetacoplan who experience a BTH event will have a temporary dose increase. The company presented an analysis of haemolysis events in the PEGASUS study by Latour et al. (2024). It calculated that 9 out of 19 (47%) people experienced a BTH event that was not associated with a complement-amplifying condition. So, the company considered that these

events would be treated with a permanent dose escalation. Based on this, it updated its base case after the first committee meeting to assume that 53% of people having pegcetacoplan who experience a BTH event have temporary dose escalation for 3 cycles (12 weeks). The EAG stated that it was unclear how the company obtained the figure of 53% from the Latour et al. (2024) study. It also highlighted that according to the BTH event management flowchart from Griffin et al. (2024a), there is a possibility of BTH events being observed without any dose escalation. This had not been modelled by the company. The EAG preferred to model the proportion of people experiencing a BTH event who temporarily escalate dose based on Griffin et al. (2024a), which reported the management of 18 BTH events that were not managed within clinical trials. It calculated that in Griffin et al. (2024a), 14 of the 18 (78%) BTH events resulted in either no dose escalation or a temporary dose escalation. The EAG noted that there was not an option for no dose escalation in the economic model. It preferred to assume that 78% of BTH events result in temporary dose escalation but considered this could still substantially overestimate treatment costs for pegcetacoplan. This is because the BTH rate does not reduce over time, and the modelling does not account for events with no dose escalation. The company stated that 1 of the 18 people in the Griffin et al. (2024a) study was already on the maximum dose so further dose escalation would not have been an option. As a result, 13 of the 18 (72%) people had either no dose escalation or temporary dose escalation (rather than 14 out 18). The company also stated that in current UK clinical practice, C5 inhibition on pegcetacoplan is reserved for use only in rare cases of severe BTH events. So, people having pegcetacoplan would not typically have a C5 inhibitor to treat a BTH event. This was supported by a management flowchart for BTH events in clinical practice from Griffin et al. (2024a) and was validated by 2 clinical experts consulted by the company. So, the company did not include a one-off cost of eculizumab in its base case. The committee acknowledged that a BTH event would only be treated with a single dose of eculizumab in rare cases. So it concluded it was appropriate not to include a one-off cost for eculizumab in the economic modelling. It considered that BTH events would either be treated with no dose escalation, temporary dose escalation or a permanent dose escalation. But, it noted that there was uncertainty about the proportions for each treatment option. It concluded that it preferred to assume 72% of BTH events for people having pegcetacoplan would be treated with a temporary dose escalation for 12 weeks and 28% with a permanent dose escalation.

Long-term discontinuation probabilities

3.11 In the company's base case, the treatment discontinuation rate for the first year of danicopan add-on therapy was modelled in line with the ALPHA trial. For pegcetacoplan, the treatment discontinuation rate was based on the PEGASUS trial. But, the company assumed no discontinuation for weeks 1 to 16 because discontinuations in the PEGASUS trial during weeks 1 to 16 were caused by BTH. The company had clinical expert opinion that treatment dose adjustments of pegcetacoplan may be implemented for BTH events, rather than discontinuation. For weeks 17 to 52, the treatment discontinuation rate for pegcetacoplan was modelled in line with the PEGASUS trial. The company assumed 0% discontinuation for danicopan add-on therapy and pegcetacoplan after year 1, because of a lack of data on discontinuation rates beyond this timepoint. The company also added that the assumption of 0% discontinuation after year 1 was in line with TA778. The EAG acknowledged that there was a lack of data on which to base long-term discontinuation rates. But it considered it plausible that there would be a small long-term discontinuation rate for danicopan add-on therapy and pegcetacoplan. It provided a scenario that assumed a 1% discontinuation rate per cycle for both treatments. It noted that this was lower than the discontinuation rate for both treatments in the period immediately before week 52. The company noted that the EAG's scenario resulted in 56% of people in the model stopping treatment after 6 years. It considered this to lack clinical validity because extravascular haemolysis is a chronic condition and treatment with danicopan is recommended for a person's lifetime unless stopping is clinically indicated. Clinical experts stated that if a person was to stop treatment because of lack of efficacy, adverse events or issues with administration, then this would most likely happen within the first year of treatment. They considered that there would be a very small proportion of people who would stop treatment after the first year, but this would be less than 1% per cycle (as modelled in the EAG's scenario analysis). The committee agreed with the clinical expert that the 4-weekly discontinuation rate beyond 1 year would likely be between 0% and 1%. The committee acknowledged that at the time of submission, the company stated there was no data available after year 1 on which to base long-term discontinuation rates. The committee requested scenario analyses exploring the impact on cost effectiveness for the range of 4-weekly discontinuation rates beyond year 1 at the first committee meeting.

3.12 After the first committee meeting, the company provided scenarios that showed that danicopan add-on therapy becomes less cost effective as the discontinuation rate for both treatments increases. The company also reported results from Patriquin et al. (2024), where there were no discontinuations in a 48-week OLE after completion of PEGASUS, to support its base-case assumption of 0% discontinuation after year 1. It also provided data from ravulizumab for PNH (Studies 301 and 302). Data was available up to 18 months of the OLE period for both studies, which showed 4-weekly ravulizumab discontinuation rates of 0.14% and 0.08%, respectively. It stated that this suggests that the proportion of people that will discontinue over a long period of time is negligible. The EAG considered that the data from Studies 301 and 302 suggest that a 0% long-term discontinuation rate is implausible. It preferred to assume a 0.1% discontinuation rate per 4-week cycle after year 1, reflecting similarity to long-term follow up from Studies 301 and 302. The committee acknowledged that the majority of discontinuation would occur within the first year of treatment, but considered it implausible to assume 0% discontinuation after year 1. It considered that it was reasonable to model long-term discontinuation rates in line with the 4-weekly discontinuation rates in Studies 301 and 302. The committee concluded that it preferred to assume a 0.1% discontinuation rate for danicopan add-on therapy and pegcetacoplan per cycle after year 1.

Subsequent therapy after discontinuation of danicopan add-on therapy

3.13 In its initial base case, the company assumed that after stopping treatment with danicopan add-on therapy, people would switch to C5 inhibitor monotherapy. The EAG noted that pegcetacoplan is currently used for treating extravascular haemolysis, so considered that a large proportion of people who stop danicopan add-on therapy would have pegcetacoplan. The committee considered it was reasonable to assume that some people who stop danicopan add-on therapy would switch to pegcetacoplan. But there was uncertainty about the proportion of people that would be expected to switch to pegcetacoplan. The committee requested an estimate of the proportion of people who would be expected to switch to pegcetacoplan after stopping danicopan add-on therapy, with supporting data or evidence. After the first committee meeting, the company consulted a clinical expert who stated that approximately 50% to 60% of people

who stop having danicopan add-on therapy would have pegcetacoplan. But the clinical expert noted that the choice would depend on whether or not the person had had pegcetacoplan before. The company noted that this estimate aligned with estimates received by NICE as part of the clinical expert submissions. Specifically, after reweighting the proportions of subsequent treatments to only include treatments available in the ALPHA and PEGASUS trials, it was estimated that approximately 60% of people are expected to switch to pegcetacoplan. Based on this, the company's updated base case assumed that 60% of people who stopped having danicopan add-on therapy switched to pegcetacoplan. The EAG considered that the company's updated base case was an improvement from the original base case. It used the 60% estimate for its preferred assumptions but considered the parameter was still highly uncertain. The committee considered it was reasonable to assume that 60% of people who stopped having danicopan add-on therapy would switch to pegcetacoplan, in line with clinical expert opinion.

Pegcetacoplan disutility

3.14 In line with TA778, the company applied an annual disutility of 0.025 associated with the administration of eculizumab to account for the increased frequency of intravenous infusions versus ravulizumab. Because pegcetacoplan has a higher frequency of administration than ravulizumab, the same annual disutility of 0.025 was applied for pegcetacoplan in the company's base case. The company also stated that it was appropriate to apply a disutility for pegcetacoplan because of the time needed to administer it. As per the summary of product characteristics for pegcetacoplan, the administration time is approximately 30 minutes (if using 2 sites). The vial should also be brought to room temperature before use, which also takes approximately 30 minutes. The EAG highlighted that in TA778, a disutility was only applied for eculizumab but not for pegcetacoplan or ravulizumab. It preferred to remove the disutility for pegcetacoplan because there was a lack of supporting evidence for it. The committee noted that the original source for the disutility value was a discrete choice experiment study looking at the disutility associated with intravenous administration compared with oral administration. The committee recalled that danicopan is given as an add-on to a C5 inhibitor, which is administered intravenously. So, the committee was not convinced that the disutility value chosen by the company was appropriate. It

also noted that the company's approach was inconsistent with TA778, which was the source from which the disutility value was obtained. It concluded that it preferred to assume no administration-related disutility for pegcetacoplan.

Cost-effectiveness estimates

Acceptable ICER

3.15 NICE's manual for health technology evaluations notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted concerns around the high level of uncertainty, specifically:

- the comparative efficacy between danicopan add-on therapy and pegcetacoplan (see section 3.5)
- the lack of robust transition probabilities for danicopan add-on therapy and pegcetacoplan (see section 3.7)
- the short-term follow-up data for BTH events relative to the 45.7-year time horizon and the long-term BTH rate for pegcetacoplan (see section 3.8)
- the proportion of people on pegcetacoplan who would have no dose escalation, a temporary dose escalation or a permanent dose escalation to treat a BTH event (see sections 3.9 and 3.10)
- the per-cycle discontinuation rate for danicopan add-on therapy and pegcetacoplan after year 1 (see sections 3.11 and 3.12).

  Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources.

Company and EAG cost-effectiveness estimates

3.16 Because of confidential commercial arrangements for danicopan, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. The company's base case ICER for the comparison with pegcetacoplan was dominant (that is, it was more effective and less expensive). The analysis with the EAG's preferred assumptions for the comparison with pegcetacoplan was higher than the range normally considered an acceptable use of NHS resources.

The committee's preferences

3.17 As a basis for decision making, the committee preferred to use a model that:

- uses the naive transition probabilities derived from the ALPHA and PEGASUS trials for danicopan add-on therapy and pegcetacoplan, respectively (see section 3.7)
- uses the IA3 data-cut to derive transition probabilities for danicopan add-on therapy (see section 3.7)
- assumes a long-term annual BTH rate for pegcetacoplan of 10% to 18% (see section 3.8)
- assumes 72% of BTH events for people having pegcetacoplan would be treated with a temporary dose escalation for 12 weeks and 28% with a permanent dose escalation (see sections 3.9 and 3.10)
- assumes a 0.1% discontinuation rate for danicopan add-on therapy and pegcetacoplan per 4-weekly cycle after year 1 (see sections 3.11 and 3.12)
- assumes that 60% of people discontinuing danicopan add-on therapy would switch to pegcetacoplan (see section 3.13).

  The ICER for the comparison with pegcetacoplan assuming a long-term annual BTH rate for pegcetacoplan of 10% was above the lower end of the range normally considered an acceptable use of NHS resources. For the comparison with pegcetacoplan assuming a long-term annual BTH rate for

pegcetacoplan of 18%, danicopan add-on therapy was dominant (that is, it was more effective and less expensive).

Other factors

Equality issues

3.18 The committee did not identify any equality issues.

Uncaptured benefits

3.19 A stakeholder highlighted that danicopan is an oral therapy, so it would be easier for people with needle phobias or who have compromised venous access to adhere to treatment. The committee noted that danicopan is given as an add-on to eculizumab (every 2 weeks) or ravulizumab (every 8 weeks), both of which are administered as intravenous infusions. So, it considered that venous access would still be required for danicopan add-on therapy. It was aware that pegcetacoplan is usually given twice weekly by subcutaneous infusion and noted that the reduced frequency of non-oral administration associated with danicopan add-on therapy may be an uncaptured benefit. But, there was a lack of robust evidence to inform an administration-related disutility for pegcetacoplan in the economic modelling (see section 3.14). So, the committee concluded that all additional benefits of danicopan add-on therapy had already been taken into account.

Conclusion

3.20 The committee concluded that although the ICERs ranged from above the lower end of the range that NICE considers a cost-effective use of NHS resources to dominant, danicopan would likely represent a cost-effective use of NHS resources. So, danicopan is recommended as an add-on to ravulizumab or eculizumab as an option for treating PNH in adults with clinically significant

extravascular haemolysis while on treatment with a C5 inhibitor.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has PNH with clinically significant extravascular haemolysis while on treatment with a C5 inhibitor and the healthcare professional responsible for their care thinks that danicopan add-on therapy is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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 C.

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

Stephen O'Brien
Chair, technology appraisal committee C

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.

Dilan Savani
Technical lead

Alexandra Filby
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Celia Mayers
Project manager

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ISBN: 978-1-4731-6125-410