NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using danicopan in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: May 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using danicopan in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 19 June 2024
- Second evaluation committee meeting: 2 July 2024
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Danicopan is not recommended, within its anticipated marketing authorisation, as an add-on to ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults with residual haemolytic anaemia.

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 complement component 5 (C5) inhibitors eculizumab and ravulizumab. After a C5 inhibitor, people who still have anaemia (residual haemolytic anaemia) and symptoms of PNH usually have pegcetacoplan.

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. So it is unclear how well danicopan works compared with pegcetacoplan.

Because of the uncertainty in the clinical evidence and some of the assumptions used to estimate cost effectiveness, the cost-effectiveness estimates for danicopan are also uncertain. More evidence is needed to determine the cost effectiveness of danicopan, so danicopan is not recommended.

2 Information about danicopan

Anticipated marketing authorisation indication

2.1 Danicopan (Voydeya, Alexion) does not have a marketing authorisation in Great Britain yet. The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending the granting of a marketing authorisation for the medicinal product danicopan, intended 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 will be available in the summary of product characteristics for danicopan.

Price

2.3 The list price is currently confidential and cannot be reported here.

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 The current 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 (TA698). 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 have eculizumab because of preference. 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 a 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. The company positioned danicopan as an add-on to eculizumab or ravulizumab for PNH in adults with 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 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 option recommended by NICE for clinically significant extravascular haemolysis and is considered standard care for clinically significant extravascular haemolysis 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. This is due to the limitations with the naive comparison and the indirect treatment comparison (see section 3.5). The EAG did an analysis, referred to as the 'EAG-preferred 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 due to 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 a12-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/l 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 squared 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 square 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 who had haemoglobin levels 10.5 g/dl or below despite treatment with eculizumab. Before adjusting for treatment-effect modifiers or prognostic factor variables, the company created a trimmed population from the ALPHA trial population to align more closely with 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 resulting 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 resulting 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 (in line with the inclusion criteria of the ALPHA trial). 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 company also assumed an administration-related disutility for pegcetacoplan and eculizumab, which was another key driver of cost effectiveness. 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). Overall, the EAG considered that the relative efficacy estimates were too uncertain to provide an EAG base case. Further to the EAG-preferred analysis (see section 3.3), it also provided an 'EAG-preferred company base case'. This assumed equal efficacy between danicopan add-on therapy and pegcetacoplan, with transition probabilities derived from the ALPHA trial. 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. It concluded that it would prefer transition probabilities for danicopan add-on therapy to be 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 derived the per-cycle probabilities directly from the PEGASUS trial. It was assumed that the BTH-event probabilities for week 48 onwards were equal to the observed rate in the PEGASUS trial between weeks 17 and 48 (open-label period). The company assumed that because all observed BTH events in PEGASUS resulted in dose escalation, all BTH events were considered 'clinically actionable'. So all BTH events were included in the calculation of the BTH-event rate for pegcetacoplan. The company's modelling approach resulted in a higher BTH-event rate in the pegcetacoplan arm (2.53% 4-weekly rate for weeks 1 to 16 and 2.67% 4-weekly rate for week 17 onwards) compared with the danicopan add-on therapy arm (0% 4-weekly rate for weeks 1 to 24 and 0.24% 4-weekly 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 due to the differences between trial populations (see section 3.5) and 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. 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), 13 out of 48 people (27.1%) having pegcetacoplan for a mean duration of 20.2 months experienced a BTH event. In Kulasekararaj et al., 6.8% of people having ravulizumab experienced a BTH event with up to 4 years of study follow up. The EAG stated that the studies provided by the company did not address its concerns about the limitations of the naive comparison of BTH-event rates. In the EAG-preferred company base case, it assumed equal BTH-event probabilities for danicopan add-on therapy and pegcetacoplan for week 17 onwards (4-weekly rate of 0.24%). 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. They added that there are also varying severities of BTH events and the definition of a 'clinically actionable' BTH event would vary in clinical practice. The committee noted that the long-term BTH-event rates were a substantial driver of cost effectiveness. It also noted that the long-term BTH-event rates in the model were based on approximately 1-year follow up and extrapolated for the remaining time horizon. It considered that it was uncertain whether the criteria used to classify BTH events from the ALPHA trial and PEGASUS trial were comparable. It recalled that longer-term data on BTH events was available from Griffin et al.(2024a) and Kulasekararaj et al. But, it noted these were presented by the company as a percentage of people experiencing a BTH event during a specific period of time. It considered that it would be useful to see these presented as 4-weekly BTH-event rates, so they could be compared with the BTH-event rates in the model. The committee concluded that it would like to see additional evidence to support the company's assumptions about long-term BTH-event rates in the model. This should also include any detail about the specific criteria used to classify a BTH event and comparability with the criteria used in the model.

Modelling of costs associated with BTH

3.9 In the company 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 a week for the second dose escalation (in the event of a further BTH event).

Under these assumptions, most people in the pegcetacoplan arm eventually escalate to a maintenance dose of 3 times a week. The company stated that this dose-escalation regimen for BTH is in line with the approach adopted in an open-label extension (OLE) study of

pegcetacoplan. It was also confirmed by clinical experts to reflect UK clinical practice. The company added that the summary of product characteristics for pegcetacoplan supports escalation beyond the 1,080 mg twice-weekly dose. It 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 people experienced BTH events in the study. Of those, 4 (8.3%) were escalated to have pegcetacoplan every 3 days, and 2 (4.2%) were escalated to have 3 doses per week. It considered that the others may have experienced 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 of 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 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, clinicians 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, and so it would be useful to see 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. The committee concluded that it preferred a base case in which the pegcetacoplan dose increase for managing a BTH event is maintained for up to 3 months and then reduced to a maintenance dose of twice weekly (until another possible BTH event).

Long-term discontinuation probabilities

3.10 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. A clinical expert stated that if a person was to stop treatment due to 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 concluded that it would like to see scenario analyses exploring the impact on cost effectiveness for the range of 4-weekly discontinuation rates beyond year 1 that it considered plausible.

Subsequent therapy after discontinuation of danicopan add-on therapy

3.11 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. It provided a scenario assuming that 80% of people who stop danicopan add-on therapy would incur the costs associated with a twice-weekly dose of pegcetacoplan. The remaining 20% would stay on C5 inhibitor monotherapy. The EAG noted that it was only possible to model the costs of subsequent pegcetacoplan and associated BTH probability. It did not adjust any other probabilities or disutilities for people who stop danicopan add-on therapy. 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. So the committee concluded it would like to see 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. It also requested that the company update the model functionality so it is possible to model the costs and benefits of people switching to pegcetacoplan after stopping danicopan add-on therapy.

Cost-effectiveness estimates

Company any EAG cost-effectiveness estimates

3.12 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 incremental cost-effectiveness ratio (ICER) for the comparison with pegcetacoplan was dominant (that is, it was more effective and less expensive). The EAG-preferred company base case for the comparison with pegcetacoplan was higher than the range normally considered an acceptable use of NHS resources. The EAG-preferred analysis for the comparison with C5 inhibitor monotherapy was also

higher than the range normally considered an acceptable use of NHS resources.

Acceptable ICER

3.13 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 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)
- whether the criteria used to classify BTH events from the ALPHA trial and PEGASUS trial were comparable (see section 3.8)
- the short-term follow-up data for BTH events relative to the 45.7-year time horizon (see section 3.8)
- the proportion of people on pegcetacoplan who would have a single dose of eculizumab, or an increased dose of pegcetacoplan to treat a BTH event (see section 3.9)
- the per-cycle discontinuation rate for danicopan add-on therapy and pegcetacoplan after year 1 (see section 3.10)
- the proportion of people who would be expected to switch to pegcetacoplan upon stopping danicopan add-on therapy (see section 3.11).

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.

The committee's preferences

3.14 The committee preferred a model that included:

- the IA3 data-cut to derive transition probabilities (see section 3.7)
- the dose increase for the management of a BTH event for people having pegcetacoplan is maintained for up to 3 months and then reduced to a maintenance dose of twice weekly (see section 3.9).

The committee's requests for additional analyses

3.15 The committee could not arrive at a preferred ICER because of the high levels of uncertainty in the modelling assumptions. Particularly the transition probabilities, the BTH-event probabilities and BTH-event management costs. The committee would like to see the following additional exploratory or confirmatory work:

- Updated transition probabilities for danicopan add-on therapy derived from the IA3 data-cut of the ALPHA trial (see section 3.7).
- 4-weekly BTH-event rates from Griffin et al. (2024a) and Kulasekararaj et al. (2023) for pegcetacoplan and ravulizumab, respectively (see section 3.8).
- Additional evidence or data to support the company's assumptions about long-term BTH-event rates in the model. This should also include any detail about the specific criteria used to classify a BTH event and comparability with the criteria used in the model (see section 3.8).
- Data on the proportion of people for whom a BTH event is treated with single dose eculizumab, or by increasing pegcetacoplan dose (see section 3.9).
- Scenario analyses exploring the impact on cost effectiveness for the range of 4-weekly discontinuation rates beyond year 1 that the committee considered plausible (0% to 1%; see section 3.10).
- 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 (see section 3.11).

- Updated model functionality so that it is possible to model a proportion of people switching to pegcetacoplan after stopping danicopan add-on therapy (see section 3.11).

Other factors

Equality issues

3.16 The committee did not identify any equality issues.

Uncaptured benefits

3.17 A stakeholder highlighted that danicopan is an oral therapy. So, it would be easier for people with needle phobias or people who have compromised venous access to comply with 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 this had been captured through an administration-related disutility in the model. The committee did not identify any additional benefits of danicopan add-on therapy not captured in the economic modelling. So, the committee concluded that all additional benefits of danicopan add-on therapy had already been taken into account.

Conclusion

3.18 The committee agreed that further information was needed to decide all its preferred modelling assumptions and to understand the full impact of the uncertainties. It concluded that it was not possible to recommend danicopan as an add-on to ravulizumab or eculizumab for the treatment of PNH in adults who have residual haemolytic anaemia.

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 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
Technical adviser

Celia Mayers
Project manager

ISBN: [to be added at publication]