National Institute for Health and Care Excellence

Health Technology Evaluation

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Alexion Pharma UK	Alexion agrees that it is appropriate to refer this topic for evaluation via the Single Technology Appraisal (STA) route	Thank you for your comment. No action required.
	National PNH service England	Evaluation is appropriate as a single technology appraisal as this is the first oral proximal complement inhibitor being assessed through NICE	Thank you for your comment. No action required.
	PNH Support	In terms of addressing the criteria required for routing an evaluation through HST rather than STA, we comment as follows regarding this evaluation: 1) The prevalence of PNH is less than the required 1 in 50,000 people 2) Those PNH patients affected by extravascular haemolysis such that they would be prescribed danicopan may well be under 300 – the PNH National Service could confirm	Thank you for your comment. This topic has been routed to be appraised through the Single Technology Appraisal (STA)

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		3) PNH severely impacts quality of life 4) Danicopan could offer significant additional benefit to patients over pegcetacoplan as danicopan is an oral treatment which delivery method patients could well prefer to sub-cutaneous administration of pegcetacoplan and which could contribute to an increased quality of life (I.e. convenience of taking a pill etc)	process. No action required
Wording	Alexion Pharma UK	The wording of the remit should reflect the anticipated indication for danicopan as follows: [redacted]	Thank you for your comment. The remit has been updated. The remit is intentionally broad to ensure that it will be compatible with the wording of the marketing authorisation when it is known.
	National PNH service England	There is no information included in the draft scope in relation to current clinical trial data, where the technology will be utilised within the treatment pathway - we have addressed these within this document	Thank you for your comment. No action required.
	PNH Support	All PNH patients have an element of extravascular haemolysis and therefore this description could be more detailed to reflect the level of extravascular haemolysis it is intended to treat	Thank you for your comment. The remit is intentionally broad to ensure that it will be compatible with the wording of the marketing authorisation when it is known. No action required

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Timing Issues	Alexion Pharma UK	A timely evaluation by NICE is required to provide guidance to NHS England as soon as possible to inform national commissioning decisions given marketing authorisation for danicopan for EVH in adult patients with PNH is anticipated for [redacted]	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. No action required.
	National PNH service England	Standard assessment is acceptable	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. No action required.
	PNH Support	Patients being treated with a C5 inhibitor who experience extravascular haemolysis and have anaemia after at least 3 months of treatment with a C5 inhibitor. I have the option of treatment with pegcetacoplan which is licenced	Thank you for your comment. NICE aims to publish guidance as

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		so there is no urgency. However it may be that patients would prefer taking oral medication (albeit this would still need to be used together with a C5 infusion) instead of medication with a sub-cutaneous delivery method (i.e. pegcetacoplan). Also our current understanding as to why some PNH patients respond better to some medications rather than others is still developing therefore having more treatment options means that patients are able to access the best treatment option for them.	soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Alexion Pharma UK	Alexion would like to highlight that Danicopan as an add-on therapy to C5 inhibitor is a treatment option for extravascular haemolysis (EVH) in PNH. We believe that the background information currently presented in the draft scope is inappropriately focused on PNH in general and would therefore like to request that the content is revised to focus specifically on EVH in PNH. For example, Alexion would like to suggest replacing the first paragraph of the Background Information section with the following text (or similar): “Paroxysmal nocturnal haemoglobinuria (PNH) is a rare blood condition in which red blood cells are attacked by the body’s immune system. PNH is a chronic condition characterised by intravascular haemolysis (IVH) (rupturing of red blood cells) with resultant anaemia often leading to transfusion dependence, severe disabling symptoms of haemolysis and, frequently, thrombosis (blood clotting).	Thank you for your comment. The background section has been updated to increase the focus on EVH in PNH. We have updated the epidemiology paragraph to note that the proportion of people with PNH who experience clinically significant EVH is uncertain.

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		In addition, some PNH patients (10-20% of PNH patients) may also experience extravascular haemolysis (EVH) (haemolysis taking place in the liver, spleen, bone marrow, and lymph nodes), which can be clinically significant and lead to symptomatic anaemia and ongoing transfusion dependence. Alexion would also like to suggest that the paragraph presenting disease epidemiology information is focused on EVH in PNH rather than PNH.	
	National PNH service England	Background: There is some information omitted from this section which we have discussed below: Extravascular haemolysis only occurs in patients with PNH being treated with a C5 inhibitor (Eculizumab/Ravulizumab-the two of the comparator treatments). PNH is a life-threatening condition until treated. There are approximately 940 patients under the care of PNH service in England and Wales, however due to the significant overlap between PNH and bone marrow failure conditions, the cohort of patients with PNH requiring treatment is smaller with 291 on active complement inhibition (2021-2022 data excluding clinical trials) Danicopan is an oral factor D inhibitor, to treat patients with PNH on a C5 inhibitor experiencing extravascular haemolysis Current available clinical trial data: this is summarised below: Kulasekararaj et al: Phase 2 study of danicopan in patients with paroxysmal nocturnal hemoglobinuria with an inadequate response to eculizumab. Blood (2021) 138 (20): 1928–1938.	Thank you for your comments. The background section is intended to provide a brief summary of the condition. No action required.

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		In a phase 2 dose-finding trial, eculizumab-treated transfusion-dependent patients with PNH (n = 12) received danicopan, 100 to 200 mg three times a day, in addition to their eculizumab regimen for 24 weeks. 11/12 completed the 24-week treatment period (1 discontinued due to serious adverse event unrelated to Danicopan). Addition of danicopan resulted in a mean Hgb increase of 2.4 g/dL at week 24. In the 24 weeks prior to danicopan, 10 patients received 31 transfusions (50 units) compared with 1 transfusion (2 units) in 1 patient during the 24-week treatment period. Mean Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score increased by 11 points from baseline to week 24. The most common adverse events were headache, cough, and nasopharyngitis. Addition of danicopan, a first-in-class FD inhibitor, led to a meaningful improvement in Hgb and reduced transfusion requirements in patients with PNH who were transfusion-dependent on eculizumab. These benefits were associated with improvement of FACIT-Fatigue. Current trial awaiting reporting at EHA: Danicopan as Add-on Therapy to a C5 Inhibitor in Paroxysmal Nocturnal Hemoglobinuria (PNH) Participants Who Have Clinically Evident Extravascular Hemolysis (EVH)(ALPHA)NCT04469465. The abstract data will be available in 2 weeks	
	PNH Support	The description of danicopan does not include that it is oral and taken 3 times per day which we consider to be relevant.	Thank you for your comments. The background section is intended to provide a brief summary of the condition. No action required.

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Intervention	Alexion Pharma UK	Alexion would like to request that the intervention wording is revised to: 'Danicopan as an add-on to a C5 inhibitor (eculizumab or ravulizumab).'	Thank you for your comment. The intervention wording has been updated.
Population	Alexion Pharma UK	Alexion would like to suggest that the population wording is amended to: Adult patients with PNH who have signs and symptoms of extravascular haemolysis while on treatment with a C5 inhibitor (eculizumab or ravulizumab).	Thank you for your comment. The population wording has been updated
	Genetic Alliance UK	PNH is a rare condition that can have a significant impact on quality of life. As this technology has been routed through an STA rather than HST pathway, its evaluation may be disadvantaged by the evidence constraints of smaller population numbers therefore this would be a good case for the committee to exercise flexibility in their decision making.	Thank you for your comment. The committee will consider and discuss the strengths and limitations of the evidence and reach a judgement about the acceptability of the evidence according to the evaluation context. No action required.
	National PNH service England	Yes	Thank you for your comment. No action required.
	PNH Support	The population is stated to be estimated at 650 to 900 people in England with PNH. We believe that the number is closer to the top end of this range which can be confirmed by the PNH National Service. As this technology has	Thank you for your comment. The committee will consider

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		been routed through an STA rather than HST pathway, its evaluation may be disadvantaged by the evidence constraints of smaller population numbers therefore this would be a good case for the committee to exercise flexibility in their decision making	and discuss the strengths and limitations of the evidence and reach a judgement about the acceptability of the evidence according to the evaluation context. No action required.
Subgroups	Alexion Pharma UK	We do not foresee any subgroups that would require separate consideration.	Thank you for your comment. No action required.
	National PNH service England	No	Thank you for your comment. No action required.
	PNH Support	Patients treated with C5 inhibitors who continue to experience extravascular haemolysis resulting in suboptimal disease control are the subgroup which would benefit from this treatment.	Thank you for your comment. Danicopan will be appraised within its marketing authorisation. The company can submit relevant subgroup analyses in their submission which will be considered by the Appraisal Committee. No action required

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Comparators	Alexion Pharma UK	Pegcetacoplan is the only NICE recommended therapy for the treatment of PNH patients with anaemia that is not controlled after treatment with a C5 inhibitor (i.e. PNH patients with EVH) (Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [TA778]). Ravulizumab and eculizumab are neither licensed nor used in UK clinical practice for the treatment of EVH and therefore should not be considered as comparators in the appraisal of danicopan.	Thank you for your comment. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. This will depend on the final marketing authorisation, current clinical practice and the clinical and cost effectiveness evidence. No action required.
	Genetic Alliance UK	It is important to note that having multiple treatment options for the same condition improves patient care and outcomes. Our current understanding as to why some people respond better to some medications than others is still developing therefore having multiple options means that patients can find the best treatment option for them.	Thank you for your comment. No action required.
	National PNH service England	All three comparators listed are available within the NHS to treat PNH. Danicopan is an oral factor D inhibitor, to treat patients with PNH on a C5 inhibitor experiencing extravascular haemolysis. It is planned in combination with C5 inhibitor as a combination treatment. For patients with PNH and extravascular haemolysis, Pegcetacoplan is the only proximal complement inhibitor currently licenced that treated extravascular and intravascular haemolysis	Thank you for your comment. No action required.

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		Not all patients with extravascular haemolysis are suitable for or wish to utilise Pegcetacoplan in view of choice and also modality of administration (subcutaneous infusion twice weekly) Eculizumab and ravulizumab are current available but are C5 inhibitors, thus do not address extravascular haemolysis, thus the outcomes from treatment are different in terms of levels of anaemia, however the fundamental life-threatening PNH management is the same	
	PNH Support	Although all 3 treatments currently listed as comparators are currently licenced for use in PNH, danicopan cannot be directly compared with eculizumab or ravulizumab on their own because it is not a monotherapy. Danicopan can only be directly compared with pegcetcacoplan and only when it is used in conjunction with eculizumab or ravulizumab.	Thank you for your comment. The appraisal committee will appraise danicopan as an add-on treatment to a C5 inhibitor not as a monotherapy. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, current clinical practice and clinical and cost effectiveness evidence. No action required.

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Outcomes	Alexion Pharma UK	Of the outcome measures listed in the draft scope, it is important to note that no data on overall survival will be available from the clinical development programme and as such, we would suggest this outcome measure is removed from the scope. Further, we would like to flag that breakthrough haemolysis and thrombotic events were captured only in the context of adverse events.	Thank you for your comment. The list of outcomes in the scope aims to include the main outcomes that are relevant to estimating clinical effectiveness. The committee will consider the plausibility of any assumptions made in the economic model. No action required.
	National PNH service England	Patient productivity/earning potential	Thank you for your comment. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes as well as uncaptured benefits and non-health factors if appropriate. No action required.
	PNH Support	Additional outcome measures would be: • LDH level	Thank you for your comment. The list of outcomes in the scope

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		• Specifically in relation to HQOL, the ability of a patient on the treatment to start to work/study or return to work /study as a result of improvement in their quality of life since treatment with the drug	is not intended to be exhaustive, the appraisal committee can consider other outcomes as well as uncaptured benefits and non-health factors if appropriate. No action required.
Equality	Alexion Pharma UK	We do not envisage any equality issues related to the proposed draft remit and scope	Thank you for your comment. No action required.
	National PNH service England	All patients can access the PNH service	Thank you for your comment. No action required.
	PNH Support	Age and pregnancy are protected characteristics and if different recommendations are made for children, adults and pregnant women, this could lead to inequality. However, it is acknowledged that there is unlikely to be trial data for children and pregnant women at this stage.	Thank you. The committee will consider any equalities issues during the appraisal. No action required.
Other considerations	Alexion Pharma UK	None	Thank you for your comment. No action required.

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	National PNH service England	Dancicopan is combined with a C5 inhibitor , thus pricing structure needs to be considered	Thank you for your comment. No action required.
Questions for consultation	Alexion Pharma UK	**Q: Where do you consider danicopan with a C5 inhibitor will fit into the existing care pathway for PNH? Would danicopan with a C5 inhibitor be offered before, after or instead of pegcetacoplan?** **A:** Danicopan add-on therapy should be positioned as an alternative treatment option to pegcetacoplan. **Q: Would people with PNH have to have received an approved C5 inhibitor for at least 6 months prior to receiving danicopan?** **A:** [redacted] **Q: What is the most appropriate comparator for danicopan with a C5 inhibitor?** **A:** Pegcetacoplan is the only other treatment available in UK clinical practice for patients with EVH and is therefore the only appropriate comparator for danicopan add-on therapy. **Q: What proportion of people with PNH have extravascular haemolysis?**	Thank you. Your comments will be considered by the committee during the appraisal process. No action required.

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		A: EVH may become clinically evident in a small subset of PNH patients (estimated 10-20%) who are treated with a C5 inhibitor. **Q: How is 'high disease activity' in PNH defined?** **A:** High-disease activity is defined by elevated haemolysis (LDH ≥1.5x ULN) and the presence of related clinical symptom(s): fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin <100 g/L), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. **Q: Would danicopan be a candidate for managed access?** **A:** Alexion does not consider danicopan to be a candidate for managed access. **Q: Do you consider that the use of danicopan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **A:** Through presentation of a cost-effectiveness analysis Alexion will aim to capture all relevant benefits that can be expressed within the QALY calculations whilst being adherent to the NICE reference case. Considering the nature of the condition it may be that additional benefits cannot be captured due to a scarcity of data. Where this is the case, Alexion will indicate in its submission for consideration during the appraisal.	

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		Q: Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. **A:** Data from the ALPHA study which is a multi-region, randomised, placebo-controlled, double blind phase 3 trial investigating the efficacy and safety of danicopan as add-on therapy to a C5 Inhibitor in PNH participants who have clinically evident EVH.	
	National PNH service England	**Where do you consider danicopan with a C5 inhibitor will fit into the existing care pathway for PNH? Would danicopan with a C5 inhibitor be offered before, after or instead of pegcetacoplan?** It would be offered at the same time as Pegcetacoplan. Some patients are not suitable for pegcetacoplan, and some patients do not wish to self inject treatment. Thus it would be considered a patient choice. **Would people with PNH have to have received an approved C5 inhibitor for at least 6 months prior to receiving danicopan?** Yes **What proportion of people with PNH have extravascular haemolysis?** 70%; those with clinically significant extravascular haemolysis is 30-40% **How is 'high disease activity' in PNH defined?** This is not completely defined, however in our clinical opinion it would include LDH >2x upper limit normal, high reticulocyte count (over 100x10*9/l),	Thank you. Your comments will be considered by the committee during the appraisal process. No action required.

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		thrombosis related to PNH, transfusion requirement and associated with patient reported symptoms (fatigue) **Would danicopan be a candidate for managed access?** Yes **Do you consider that the use of danicopan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Patient productivity and contributions to work **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** **• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which danicopan will be licensed;** **• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** **• could have any adverse impact on people with a particular disability or disabilities.**	

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		All these people would be able to access treatment if considered appropriate	
	PNH Support	**Where do you consider danicopan with a C5 inhibitor will fit into the existing care pathway for PNH?** We understand it will be offered to patients who are being considered for treatment with pegcetacoplan. Patients may prefer taking an oral medication rather than a sub-cutaneous medication (pegcetacoplan). **Would danicopan with a C5 inhibitor be offered before, after or instead of pegcetacoplan?** We understand it will be offered to patients at the same time as pegcetacoplan. **Would people with PNH have to have received an approved C5 inhibitor for at least 6 months prior to receiving danicopan?** We understand that this is the case. **What is the most appropriate comparator for danicopan with a C5 inhibitor?** Pegcetacoplan (as it is the only licenced therapy which addresses extra-vascular haemolysis) **What proportion of people with PNH have extravascular haemolysis?** The PNH National Service would be the appropriate stakeholder to confirm this. It should be noted that all PNH patients have an element of extravascular haemolysis.	Thank you. Your comments will be considered by the committee during the appraisal process. No action required.

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		How is 'high disease activity' in PNH defined? High disease activity in PNH is defined by LDH ≥ 1.5 × ULN and history of major adverse vascular events (MAVEs; including thrombotic events [TEs]); anemia; and/or physician-reported abdominal pain, dyspnea, dysphagia, erectile dysfunction, fatigue, and/or hemoglobinuria. https://pubmed.ncbi.nlm.nih.gov/35390189/ **Would danicopan be a candidate for managed access?** Yes **Do you consider that the use of danicopan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** A patient (and also potentially their carer) could start to work/study or return to work/study/caregiving duties following receipt of this treatment which would reduce/remove any required support by the state which may have previously been required. It is assumed that transfusions and hospital visits/in-patient stays as a result of uncontrolled symptoms and anaemia from extravascular haemolysis is included in the QALY otherwise these costs could be quantified as savings if a patient using danicopan no longer needed these to be addressed. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The PNH National Service (and PNH Support) could obtain data from patients on the trials for danicopan (and their carers) about their quality of life since receiving the medication, in particular any change in their ability to work/study/undertake caregiving duties.	

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		The PNH National Service could also quantify the cost of blood transfusions, in-patient stays, additional outpatient visits to address uncontrolled symptoms and anaemia resulting from extravascular haemolysis	
Additional comments on the draft scope	Alexion Pharma UK	The following statement is repeated twice in lines 3 and 4 of the paragraph titled 'The technology'; please could you remove the duplication: "in combination with either eculizumab or ravulizumab"	Thank you for your comment. In the ALPHA trial participants were randomized to receive danicopan or placebo in addition to their C5 inhibitor (eculizumab or ravulizumab) therapy. No action required

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

N/A