National Institute for Health and Care Excellence

Health Technology Evaluation

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]
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	Roche	The appraisal of crovalimab is appropriate. Given the expectation that crovalimab will have similar health benefits at a similar or lower overall costs to current treatment options, we propose that the cost comparison assessment route would be suitable for this appraisal.	Thank you for your comment. No action is needed.
	NHSE	Evaluation is appropriate as a single technology appraisal as this is the first subcutaneously administered terminal complement inhibitor being assessed through NICE	Thank you for your comment. No action is needed.
	PNH Support	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. This is the first sub-cutaneous C5 inhibitor monotherapy for PNH to be reviewed by NICE.	Thank you for your comment. The committee will consider all evidence available to them during the appraisal. No action is needed.

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Wording	Roche	The wording of the remit is appropriate.	Thank you for your comment. No action is needed.
	NHSE	There is no information included in the draft scope in relation to current clinical trial data for Crovalimab, where the technology will be utilised within the treatment pathway - we have addressed these within this document	Thank you for your comment. The scope is intended to summarise the background information for PNH and crovalimab briefly. No action is needed.
	PNH Support	Some patients experience additional symptoms as well as breakthrough haemoloysis despite treatment with complement inhibitors including fatigue which can be debilitating and impact their quality of life (both physical and psychological) including their ability to work, study, provide caregiving or take part in family life. No clinical trial or proposed label data has been included in the scope, nor does it include any information about cost effectiveness or quality of life data.	Thank you for your comments. The scope is intended to summarise the background information for PNH and crovalimab briefly. No action is needed.
Timing Issues	Roche	We believe that the proposed timelines are in line with expected marketing authorisation.	Thank you for your comment. No action is needed.

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	NHSE	Not urgent and suggested time scales are appropriate, as patients have treatment options available which are NICE approved	Thank you for your comment. No action is needed.
	PNH Support	There are already two licenced and available C5 inhibitors (eculizumab or ravulizumab) so there is no urgency however the delivery method of both these C5 inhibitors is by intravenous infusion (either 2 weekly or 8 weekly). Depending on the label and whether this treatment will be available to both C5 inhibitor naïve patients as well as those already treated with a C5 inhibitor treatment, both groups may prefer a sub-cutaneous treatment delivery method compared to eculizumab or ravulizumab. A sub-cutaneous delivery method would allow patients the freedom to travel as well as independence from homecare visits (for infusions) which can be disruptive to work, study and family life. It is also important to note that having multiple treatment options for the same condition improves patient care and outcomes. 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.	Thank you for your comment. No action is needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche	We propose that additional information is included under the technology heading, "Crovalimab is a novel anti-C5 recycling monoclonal antibody designed with a half-life, solubility, and bioavailability that supports low-volume, every-4-weeks SC administration"	Thank you for your comment. NICE no longer includes detailed information on the mechanism of action of

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		The reference for the following statement should be number 5: “Eculizumab, a C5 inhibitor, is commissioned for PNH with high disease activity”	the treatment within the scope. The reference number has been updated in the scope document.
	NHSE	Yes appropriate and complete.	Thank you for your comment. No action is needed.
	PNH Support	The description of crovalimab does not include that it is a sub-cutaneous injection used every 4 weeks which we consider to be relevant. Some patients experience additional PNH symptoms as well as breakthrough haemoloysis despite treatment with complement inhibitors including fatigue which can be debilitating and impact their quality of life (both physical and psychological) including their ability to work, study or take part in family life.	Thank you for your comment. The scope is intended to summarise the background information for PNH and crovalimab briefly. No action is needed.
Population	Roche	The population is defined appropriately as it captures the population covered by the proposed wording of the crovalimab marketing authorisation.	Thank you for your comment. No action is needed.
	NHSE	PNH is a rare haemolytic and thrombotic condition. We have approximately 1000 patients within our service, with 406 patients on complement inhibition: 342 Ravulizumab, eculizumab or Pecetacoplan (NHS funded) and 64 within clinical trials (including patients on Crovalimab).	Thank you for your comment. No action is needed

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Subgroups	Roche	The subgroups listed in the scope are appropriate for consideration.	Thank you for your comment. No action is needed.
	NHSE	None, although some patients (rare) who do have difficulty in intravenous access might have benefit from subcutaneous injection.	Thank you for your comment. No action is needed.
	PNH Support	Patients treated (or to be treated) with licenced C5 inhibitors (infusions) who would prefer a sub-cutaneous delivery method are the subgroups which would benefit most from this treatment.	Thank you for your comment. No action is needed.
Comparators	Roche	We believe that eculizumab and ravulizumab are considered relevant comparators (C5 inhibitors) and standard of care for the treatment of PNH in the NHS.	Thank you for your comment. NICE agrees that pegcetacoplan, iptacopan and danicopan are not appropriate comparators for crovalimab and have removed these from the scope.
	NHSE	All three comparators listed are available within the NHS to treat PNH. Two additional treatments (Danicopan and Iptacopan) are also undergoing NICE TA.	Thank you for your comment. Please note, the list of comparators was updated.

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	PNH Support	Two of the comparators stated in the draft scope are described as 'subject to a NICE ongoing appraisal', therefore they are not widely available. As far as we understand, the definition of a comparator is a technology that is routinely used in the NHS, therefore we have concerns that these comparators appear to be outside of the usual definition of a comparator. We understand that there may be circumstances that are appropriate to use technologies that are currently being assessed by NICE as a comparator but we would appreciate an overview of how decisions about expanding the definition of a comparator are made, and a discussion with the patient community as to the potential risks and benefits of using comparators outside of the definition and when it may be appropriate to do so. Otherwise, we fear this may lead to an inconsistency and inequality between appraisals. The following named comparators only address intravascular haemolysis so therefore would be suitable comparators to crovalimab which, also only addresses intravascular haemolysis: • eculizumab • ravulizumab The following named comparator addresses both intravascular haemolysis and extravascular haemolysis and therefore would not be a suitable comparator for crovalimab which only addresses intravascular haemolysis: • pegcetacoplan The following named comparators address both intravascular haemolysis and extravascular haemolysis when used together, so would not be a relevant comparator for crovalimab which only addresses intravascular haemolysis: • danicopan with a C5 inhibitor (subject to NICE ongoing appraisal - see comments above)	Thank you for your comments. NICE agrees that pegcetacoplan, iptacopan and danicopan are not appropriate comparators for crovalimab and have removed these from the scope.
Outcomes	Roche	Given the intention to submit following the cost-comparison process, evidence on overall survival will not be provided.	Thank you for your comment.

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		Haemoglobin should be replaced with “stabilised haemoglobin” The other listed outcomes capture the most important health-related benefits and harms for people with PNH.	At this stage of the evaluation, terminology to describe outcomes is kept inclusive. So, no action is needed.
	NHSE	Yes Additional outcomes could be treatment satisfaction and patient reported outcomes	Thank you for your comments. Treatment satisfaction and patient reported outcomes can be considered as part of the health-related quality of life outcome. No action is needed.
	PNH Support	Additional outcome measures would be: • LDH level Specifically in relation to HRQOL: • 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 or as a result of the convenience of using a 4 weekly self-administered sub-cutaneous injection (so time off work is not required in order to receive an infusion) is very relevant. We consider that the EQ 5D 5L questionnaire is not specific enough to collect relevant information about those who have been able to start working, or work more, start studying or study more, since starting treatment. It asks about “USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)”. If work or study hadn’t been a “usual activity” for someone prior to treatment then this question doesn’t capture the fact of someone who can now: work; work more; study; study	Thank you for your comments. LDH level was measured as a key outcome in the clinical trials assessing crovalimab. LDH level has been added as an outcome in the scope. The committee will consider the appropriateness of measures of health-

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		more, since starting treatment which we consider has bearing on the benefit of this treatment to the patient and the State. • burden of treatment should also be considered as part of this technology appraisal. Current licenced treatment options for treatment naïve patients are limited to intravenous infusions which can: • cause damage to veins and be distressing to receive if veins are damaged from repeated infusions; • be disruptive to their work, study, travel or family life more generally • In relation to adverse effects of treatment, the risk and treatment of type 3 hypersensitivity should be considered i.e. when a patient who has already been treated with a C5 inhibitor changes to another C5 inhibitor and may experience a reaction after the switch from one drug to the other.	related quality of life during appraisal.
Equality	Roche	No equality issues have been identified.	Thank you for your comment. No action is needed.
	NHSE	All PNH patients in England can access the two PNH centres for management of PNH (Leeds and London)	Thank you for your comment. We have added your comment to the Equality Impact Assessment form.
	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 will not be trial data at this stage for children and pregnant women.	Thank you for your comment. We have added your comment to the Equality

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			Impact Assessment form.
Other considerations	Roche	No comments.	Thank you for your comment. No action is needed.
	NHSE	None	Thank you for your comment. No action is needed.
Questions for consultation	Roche	**Where do you consider crovalimab will fit into the existing care pathway for paroxysmal nocturnal haemoglobinuria?** As Crovalimab has been demonstrated to be non-inferior to eculizumab with a comparable safety profile, it presents an alternative C5i for PNH patients naïve to complement inhibitors and complement inhibitor-experienced patients. The long half-life and high bioavailability of crovalimab enable low-volume, every-4-week SC administration with the option for self-administration by patient or caregiver that can reduce treatment burden. Therefore, crovalimab may offer an important new treatment option for patients with PNH that provides increased freedom from their disease. **Is pegcetacoplan a relevant comparator for crovalimab in people with PNH currently treated with complement inhibitors?** Pegcetacoplan is a C3 proximal complement inhibitor and did not demonstrate non-inferiority to eculizumab for change in LDH level. The safety and efficacy of C5 inhibitors are well established, with 15 years of real-world experience unlike the newly approved C3 inhibitor, which lacks an established safety profile. Extravascular hemolysis is clinically relevant only in a subset (25-50%) of patients receiving C5 inhibitor treatment. Pegcetacoplan is recommended only as an option for treating PNH in adults who have	Thank you for your comments. NICE agrees that pegcetacoplan is not an appropriate comparator for crovalimab. Pegcetacoplan has been removed as a comparator from the scope.

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		anaemia after at least 3 months of treatment with a C5 inhibitor. Therefore, Pegcetacoplan is not a relevant comparator for crovalimab. **Would crovalimab be a candidate for managed access?** We don't anticipate that crovalimab would be a suitable candidate for managed access given the evidence already available from the commodore studies. **Do you consider that the use of crovalimab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Benefits linked to the convenience provided by crovalimab's subcutaneous administration are unlikely to be fully captured in the QALY calculations. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The efficacy and safety data for naive and switch patients was captured in the COMMODORE 1 and 2 clinical trials. **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 the treatment will be licensed;**	

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		• **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.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** Please see the response in the equality section. **NICE is considering evaluating this technology through its cost comparison evaluation process.** **NICE's health technology evaluations: the manual states the methods to be used where a cost comparison case is made.** • **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?** Crovalimab is expected to have similar efficacy to other C5-inhibitors, and be associated with similar resource use. Crovalimab will be administered subcutaneously, unlike eculizumab and ravulizumab which are administered intravenously. • **Will the intervention be used in the same place in the treatment pathway as the comparator(s)?** We expect crovalimab to be used at the same position as other C5-inhibitors in the treatment pathway.	

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		• **Have there been any major changes to the treatment pathway recently? If so, please describe.** No • **Will the intervention be used to treat the same population as the comparator(s)?** Yes (same population as eculizumab and ravulizumab) **Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** The results of the COMMODORE studies demonstrate that crovalimab is non-inferior to eculizumab, in terms of efficacy and safety. • **Would it be appropriate to use the cost-comparison methodology for this topic?** Yes. It would be appropriate to appraise crovalimab using the cost-comparison methodology.	
	NHSE	**Questions for consultation** **Where do you consider crovalimab will fit into the existing care pathway for paroxysmal nocturnal haemoglobinuria?** There are two approved terminal complement inhibitors currently for PNH and both are intravenously (IV) treatments, given either 2 weekly or every 8 weekly. Crovalimab is the first subcutaneous administered terminal complement inhibitor, but with similar efficacy to eculizumab and ravulizumab. Patients who have difficult access issues/difficult to cannulate and patient wanting to have self-care/independence will possibly choose crovalimab. This will give choice for new patients either to receive Ravulizumab (iv 8 weekly) or Crovalimab (sc 4 weekly). Additionally, patients stable on Ravulizumab or getting any issues related to access, have the ability to switch to Crovalimab in view of the modality of administration with similar efficacy.	Thank you for your comments. NICE agrees that pegcetacoplan is not an appropriate comparator for crovalimab. Pegcetacoplan has been removed as a comparator from the scope.

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		Is pegcetacoplan a relevant comparator for crovalimab in people with PNH currently treated with complement inhibitors? No. Pegcetacoplan is only available treatment choice for patients currently treated with eculizumab/ravulizumab and remain anaemic with Hb <10.5 g/l. Crovalimab will be used in patients who are stable (with no clinical evidence of extravascular haemolysis) on Eculizumab/Ravulizumab and wanted to switch to subcutaneous injections (Crovalimab) given every 4 weeks. **Would crovalimab be a candidate for managed access?** Yes **Do you consider that the use of crovalimab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Unlikely, although the modality of administration and thereby the treatment satisfaction/independence from 8 weekly/2 weekly IV treatment needs to be considered. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Clinical trial data of Crovalimab (Phase 2 and 3 data), which has been published and presented in number of meetings in abstract form. https://pubmed.ncbi.nlm.nih.gov/37421604/- Efficacy and safety of the C5 inhibitor crovalimab in complement inhibitor-naive patients with PNH (COMMODORE 3): A multicenter, Phase 3, single-arm study https://pubmed.ncbi.nlm.nih.gov/37321625/- Crovalimab treatment in patients with paroxysmal nocturnal haemoglobinuria: Long-term results from the phase I/II COMPOSER trial https://pubmed.ncbi.nlm.nih.gov/31978221/- The complement C5 inhibitor crovalimab in paroxysmal nocturnal hemoglobinuria	

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		https://library.ehaweb.org/eha/2023/eha2023-congress/387881/alexander.rth.the.phase.iii.randomized.commodore.2.trial.results.from.a.html - THE PHASE III, RANDOMIZED COMMODORE 2 TRIAL: RESULTS FROM A MULTICENTER STUDY OF CROVALIMAB VS ECULIZUMAB IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) PATIENTS NAIVE TO COMPLEMENT INHIBITORS https://journals.lww.com/hemasphere/Fulltext/2023/08003/S183__PHASE_III_RANDOMIZED,_MULTICENTER,.85.aspx-PHASE III RANDOMIZED, MULTICENTER, OPEN-LABEL COMMODORE 1 TRIAL: COMPARISON OF CROVALIMAB VS ECULIZUMAB IN COMPLEMENT INHIBITOR-EXPERIENCED PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)	
	PNH Support	How will breakthrough haemolysis be dealt with on this treatment?	Thank you for your comments. Breakthrough haemolysis is one of the outcomes of this appraisal. No action is needed.

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

Alexion Pharma UK (comparator)
Novartis Pharmaceuticals UK limited (comparator)