National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Wording	Alexion	Yes	Comment noted. No change to the scope required.
	NHS England and Improvement	The remit does reflect the clinical and cost effectiveness issues relating to this technology	Comment noted. No changes to the scope required.
	PNH NHSE-funded National Service - Leeds	Patients are keen to access this treatment as soon as possible and be able to live much more independent and productive lives by virtue of only having 8 weekly infusions. This will in turn free up NHS resource currently committed to the management and oversight of the 2 weekly Eculizumab infusions. This is especially relevant in the current COVID 19 climate where patients have been shielding and minimising contact with others and therefore visits by nurses every 2 weeks to provide infusions exposes them to an element of risk.	Comment noted. The technology will be appraised within its marketing authorisation. No change to the scope required.
	King's National PNH service	Yes agree, there is a clinical need for ravulizumab for patients with PNH and need for evaluating/scoping this	Comments noted. No changes to the scope required.

Section	Consultees	Comments	Action
Timing Issues	Alexion	The scoping process for ravulizumab for the treatment of PNH has already been subject to significant delay. Ravulizumab, which received European Marketing Authorisation for the treatment of PNH in July 2019, addresses several areas of unmet need in the management of patients with PNH and also has the potential to deliver cost savings to NHS England compared with eculizumab. It is imperative therefore that this re-scope exercise and the subsequent NICE appraisal process is completed in a timely manner to provide NHS England with appropriate guidance to inform its national commissioning decisions.	Comment noted. This evaluation has been scheduled into the Technology Appraisals work programme.

Section	Consultees	Comments	Action
	NHS England and Improvement	This is a timely appraisal	Comment noted. This evaluation has been scheduled into the Technology Appraisals work programme.
	PNH National Service (Leeds and Kings)	Patients with PNH are currently treated with eculizumab. There has been a prolonged delay in the evaluation of ravulizumab. It is urgent to resolve this as soon as possible.	Comment noted. This evaluation has been scheduled into the Technology Appraisals work programme.
	King's National PNH service	Although patients with PNH currently have benefit of treatment with eculizumab, there is a need of alternate effective treatments for PNH but ones which are extremely less burdensome for patients (i.e ravulizumab given 8 weeks versus 2 weekly for eculizumab)	Comment noted. This evaluation has been scheduled into the Technology Appraisals work programme.
Additional comments on the draft remit	NHS England and Improvement	The remit does not reference the burden on the patient in relation to treatment frequency; the standard treatment with eculizumab is a fortnightly infusion compared to an eight weekly infusion with ravulizumab.	Comment noted. The remit outlines the disease, the patients and the technology that will be covered by the evaluation.The committee will consider all relevant potential benefits of ravulizumab. No changes to the scope required.
	PNH National Service (Leeds and Kings)	The review and amendments of the comparator are appropriate and considered. They recognise and address the concerns of all the stake holders to the comparator in the initial scope.	Comments noted. no changes to the scope required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background	Alexion	The sentence ‘ Ten-year survival after diagnosis has been estimated to range between 65% and 78%’ relates to historic survival without treatment with eculizumab and should therefore be re-stated as ‘Ten-year survival after diagnosis and without treatment with a complement-inhibitor has been estimated to range between 65% and 78%.’ In addition, the background section states that there is currently no NICE guidance for treating PNH. While this is indeed the case, it is a function of the fact that at the time of marketing authorisation of eculizumab, NICE was not undertaking evaluations of technologies for ultra-orphan conditions. As such, eculizumab underwent an alternative route of assessment of appropriateness for use in the NHS and was approved for routine commissioning as outlined in the NHS England Service Specification ‘Paroxysmal nocturnal haemoglobinuria service (Adults and Adolescents)’ We therefore believe additional text should be added to the background section to reflect the above.	Comments noted. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. The scope has been updated to reflect some of the comments. Eculizumab is listed as a comparator in the scope.
	NHS England and Improvement	The background information is accurate. It would be helpful to have more detail regarding the lived experience of this disease	Comments noted. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. No changes to the scope required.

Section	Consultees	Comments	Action
	PNH National Service (Leeds and Kings)	The Background information is accurate. The only comment is that rather than most patients with PNH "not being eligible for treatment." It would be preferable to say that most patients "do not require treatment with anti-complement therapy"	Comments noted. The wording in the scope has been changed to reflect the comment.
	King's National PNH service	Few inaccuracies 1. Risk of thrombosis is high in patients with PNH (up to 40%) and is further increased in pregnant PNH patients 2. Although there is no NICE guidance for PNH treatment, eculizumab has been used and commissioned through the NHSE specialised commissioning for PNH patients since 2008 https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf	Comments noted. The scope has been updated to reflect some of the comments. Eculizumab is listed as a comparator in the scope.
The technology/ intervention	Alexion	We suggest amending the sentence: 'It is administered by intravenous infusion' by adding to the end of the sentence 'every 8 weeks during maintenance treatment'	Comment noted. The technology section of the scope briefly describes the technology of interest and does not usually include details of dosing. No change to the scope required.
	NHS England and Improvement	The description of the technology is accurate	Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
	PNH Support	Should the description not include that the therapy is an 8 weekly intravenous infusion?	Comment noted. The technology section of the scope briefly describes the technology of interest and does not usually include details of dosing. No change to the scope required.
	PNH National Service (Leeds and Kings)	The description of the technology is correct but fails to mention the key advantages of ravulizumab compared to the standard of care, eculizumab. These are that ravulizumab is only delivered once every 8 weeks compared to once every two weeks. This has major potential advantages for the NHS as well as for patients. Secondly approximately 20% of patients on eculizumab require a higher dose which is not necessary for ravulizumab.	Comment noted. The technology section of the scope briefly describes the technology of interest and does not usually include details of dosing. No change to the scope required.
Population	Alexion	Yes, the population presented reflects the licensed indication for ravulizumab in PNH.	Comment noted. No change to the scope required.
	PNH Support	Ravulizumab may be most appropriate for treating a subset of patients with PNH i.e. adults who respond well to a C5 inhibitor and don't have additional unmet need i.e. extra-vascular haemolysis.	Comment noted. The technology will be appraised within its marketing authorisation. No change to the scope required.
	NHS England and Improvement	The description of the population is accurate	Comment noted. No change to the scope required.

Section	Consultees	Comments	Action
	King's National PNH service	Yes, the population is defined accurately as per the clinical trial inclusion criteria. PNH patients not included in the trial data and hence should be considered separately are patients <18 years, patients who are pregnant and patients not on stable doses of eculizumab/and not well controlled with eculizumab	Comment noted. The technology will be appraised within its marketing authorisation. No change to the scope required.
	PNH National Service (Leeds and Kings)	The population is appropriate but is not clearly defined. This should follow the NHSE approved indications for eculizumab in PNH. (https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf)	Comment noted. The technology will be appraised within its marketing authorisation. No change to the scope required.
Comparators	Alexion	Eculizumab is the appropriate comparator for the appraisal of ravulizumab in PNH.	Comment noted. No changes to the scope required.
	NHS England and Improvement	The treatments listed are the appropriate comparators	Comment noted. No changes to the scope required.
	PNH National Service (Leeds and Kings)	Eculizumab as the comparator is appropriate. This has been available for patients in the UK since 2008, and has been used as a comparator in the clinical trials with ravalizumab.	Comment noted. No changes to the scope required.
	PNH Support	The standard treatment used in the NHS is eculizumab, and therefore appropraite	Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
	King's National PNH service	Yes, eculizumab is the standard treatment used in the PNH services for patients in need of treatment	Comment noted. No changes to the scope required.
Outcomes	Alexion	Yes	Comments noted. No change to the scope required.
	PNH Support	Under "Impact of the technology beyond direct health benefits," we comment that: as this therapy is delivered intravenously every 2 months compared to Eculizumab (which should be the comparator) which is delivered intravenously every 2 weeks, patients are not reminded that they have PNH for 2 months at a time which has a significant psychological impact. Two monthly infusions also permit less disruption to patients' and carers' employment and associated issues and family life generally. Patient access to treatment with Ravlizumab's 8 weekly infusions will free up NHS resource currently committed to the management and oversight of the 2 weekly Eculizumab infusions.	Comments noted. The committee will consider all potential benefits of the technology throughout the course of the evaluation. No change to the scope required.
	PNH National Service (Leeds and Kings)	The outcomes listed are appropriate for this evaluation	Comment noted. No change to the scope required.
	NHS England and Improvement	The description of the outcomes is appropriate	Comment noted. No change to the scope required.

Section	Consultees	Comments	Action
Economic Analysis	Alexion	• A cost-utility model will be presented that makes use of the breadth of data supporting the comparison of ravulizumab to eculizumab using an NHS perspective, modelled over a lifetime horizon • A supporting analysis where effectiveness is assumed equal consistent with the non-inferiority trial designs will also be presented comparing ravulizumab to eculizumab • The state transition model includes health states designed in consultation with clinical experts and aligned to the outcomes from the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies, and these include incomplete C5 inhibition-related or CAC – related BTH events, transfusions and spontaneous remission • Efficacy outcomes are taken from the ALXN1210-PNH-301 and ALXN1210-PNH-302 study and extrapolated to a lifetime. Remission rates are sourced from the literature. Mortality is assumed equivalent to the general population in the base case. Resource use and costs are taken from relevant, published literature. • Patient utilities within the cost-utility analysis were calculated by applying a published mapping algorithm to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ–C30) data within the studies to map to EQ-5D-3L utilities • As the treatment burden of having frequent infusions was not captured in the studies, due to the trial design, the benefits of the 8-weekly rather than 2-weekly administration frequency were derived from a discrete choice experiment using a sample of the UK general population (*comments received in response to June 2020 STA rescope consultation)	Comments noted. The committee will consider the relevant costs and benefits of ravulizumab in this appraisal. No changes to the scope required.

Section	Consultees	Comments	Action
	PNH National Service (Leeds and Kings)	Ravulizumab is likely to be less expensive than eculizumab which the HTA will address; requirement for healthcare staff time is significantly less, reducing healthcare visits from 24 per year to 6-7. This in an era of the COVID-19 pandemic would have reduced the risk of patients many of whom were shielding	Comments noted. The committee will consider the relevant costs and benefits of ravulizumab in this appraisal. No changes to the scope required.
	King's National PNH service	Unable to comment on the economic analysis and cost impact, but the impact of infrequent infusions (8 weekly, 6 times/year) will have a significant bearing on the productivity of both patients and carers.	Comments noted. The committee will consider the relevant costs and benefits of ravulizumab in this appraisal. No changes to the scope required.
	NHS England and Improvement	The economic analysis is reasonable but should take into account the small patient cohort	Comment noted. the committee can consider any relevant issues relating to the rarity of the condition.
Equality and Diversity	Alexion	We do not envisage any equality issues related to the proposed draft remit and scope	Comment noted. No change to the scope 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. We do not believe Ravulizumab has not been licenced for under 18 year olds.	Comment noted. Ravulizumab will be appraised within its marketing authorisation. The impact of any recommendation for ravulizumab on groups of people with protected characteristics will be considered by the committee. No change to the scope required.

Section	Consultees	Comments	Action
	NHS England and Improvement	Paroxysmal nocturnal haemoglobinuria is a very rare disease and patients in England benefit from two national expert centres. We are not aware of any specific access issues relating to people with protected characteristics or that commissioning this drug would disadvantage any groups.	Comment noted. No changes to the scope required.
	PNH National Service (Leeds and Kings)	The standard of care for PNH is eculizumab which is given every two weeks by intravenous infusion. This is burdensome for patients whereas ravulizumab is given every 8 weeks. Vulnerable patients, for example elderly patients, find the less frequent infusions more manageable It also allows people of working age to increase productivity due to less frequent infusions and time off work	Comment noted. Ravulizumab will be appraised within its marketing authorisation. The impact of any recommendation for ravulizumab on groups of people with protected characteristics will be considered by the committee. No change to the scope required.
	King's National PNH service	PNH patients not included in the trial data and hence should be considered separately are patients <18 years, patients who are pregnant and patients not on stable doses of eculizumab/and not well controlled with eculizumab	Comment noted. Ravulizumab will be appraised within its marketing authorisation. The impact of any recommendation for ravulizumab on groups of people with protected characteristics will be considered by the committee. No change to the scope required.

Section	Consultees	Comments	Action
Innovation	Alexion	Due to the difficulty in quantifying the full impact of breakthrough haemolysis and the treatment burden (particularly on carers), some health-related benefits of ravulizumab treatment are likely to exist outside the QALY calculations. This includes a difficulty in identifying long-term data on complications associated with breakthrough haemolysis, such that the potential benefit of more effective treatment on long-term morbidity and mortality will not be captured by the QALY calculations. Compared to the 2-weekly eculizumab regimen, the 8-weekly ravulizumab regimen lessens the treatment burden for patients by reducing the number of infusions from 26 per year to 6-7 per year, which could result in a reduced interruption of weekly routines including education and/or employment. As the treatment burden of having frequent infusions was not captured in the studies, due to the trial design, the benefits of the 8-weekly rather than 2-weekly administration frequency were derived from a discrete choice experiment using a sample of the UK general population	Comment noted. The potential innovative nature of ravulizumab and relevant potential benefits associated with the treatment will be considered by the committee throughout the evaluation. Evidence of the impact on carer quality of life can be considered by the committee. No change to the scope required.

Section	Consultees	Comments	Action
	PNH Support	This mental health benefit is significant to patients/their carers in a variety of ways including reduction of stress associated with experiencing possible breakthrough haemolysis (see below), stress/time involved in arranging the 2 weekly infusion and stress linked to their employer's reaction to the need for a 2 weekly infusion (some patients hide their condition and need for treatment from employers in order to avoid discrimination). Survey data will be provided by PNH Support to enable these benefits to be taken into account. We understand that the data for Ravulizumab evidences that patients' experience less breakthrough haemolysis than those being treated with Eculizumab which is an additional health related benefit for patients (https://doi.org/10.3324/haematol.2019.236877)	Comment noted. The potential innovative nature of ravulizumab will be considered by the committee throughout the evaluation. The impact on carers can be considered by the committee No change to the scope required.
	PNH National Service (Leeds and Kings)	Yes ravulizumab is an innovative therapy compared to eculizumab with the potential to have significant and substantial health-related benefits	Comment noted. The potential innovative nature of ravulizumab and its impact on relevant costs and benefits will be considered by the committee throughout the evaluation. No change to the scope required.
	NHS England and Improvement	This technology is innovative as patients have to take treatment every 8 weeks rather than the two weekly standard treatment with eculizumab. Both drugs are delivered by infusion so the reduction in treatment frequency is a considerable benefit to the patient, reducing the time spent in receiving healthcare and enabling the patient to have a more normal life.	Comment noted. The potential innovative nature of ravulizumab and its impact on relevant costs and benefits will be considered by the committee throughout the evaluation. No change to the scope required.

Section	Consultees	Comments	Action
	King's National PNH service	The trial data has shown non-inferiority between the proposed TA (ravulizumab) and the comparator (eculizumab), but has significant benefits from the patient perspectives including patient choice, ability to plan activities, benefit of the treatment between cycles of treatment, QOL and the frequency of infusions	Comment noted. The potential innovative nature along with the clinical and cost effectiveness of ravulizumab will be considered by the committee throughout the evaluation. No change to the scope required.
Other considerations	Alexion	None	No change to the scope required.
	PNH National Service (Leeds and Kings)	The National-funded PNH service arranges for the infusion of eculizumab every two weeks. This is difficult leading to a high dependence for patients. Moving to ravulizumab would be far more convenient for patients and would take a significant strain off the NHS. This has been even more apparent during the COVID-19 pandemic during which the delivery of 2 weekly infusions is proving to be very challenging	Comments noted. The committee will consider the relevant costs and benefits of ravulizumab in this appraisal. No changes to the scope required.

Section	Consultees	Comments	Action
Questions for consultation	Alexion	**Q.** Have all relevant comparators for ravulizumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for PNH? **A:** Yes; eculizumab, the establish standard of care for the treatment of patients in the UK with PNH, is the relevant comparator for ravulizumab. **Q:** Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or value for money, or other groups that should be examined separately? **A:** The only subgroup of patients in whom ravulizumab may provide greater clinical benefits or more value for money are those patients who are currently receiving higher than label dosing of eculizumab. However, there are no data from clinical trials in this population at present, therefore separate examination of this population is not feasible at this time. **Q:** Do you consider that there will be any barriers to adoption of this technology into practice? **A:** We do not envisage any barriers to adoption of ravulizumab, which is expected to be used in the same way as eculizumab is currently used in clinical practice.	Comments noted. No changes to the scope required. .
Additional comments on the draft scope	Alexion	None	No change to the scope required.
	PNH National Service (Leeds and Kings)	We would like to acknowledge the importance of NICE changing in comparator to eculizumab (from best supportive care) in the re-scope which makes a NICE appraisal possible.	Comment noted. No changes to the scope required.

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

None