**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]**

**Response to consultee and commentator 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**

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| Appropriateness | Apellis Pharmaceuticals | Apellis agrees that it is appropriate to refer this topic to NICE for appraisal. However, the proposed referral to the Single Technology Appraisal (STA) is not suitable and pegcetacoplan should instead be referred to NICE's Highly Specialised Technology (HST) programme. Further information is provided below regarding how pegcetacoplan meets all seven of the HST eligibility criteria. | Thank you for your comment. The routing of this topic was considered by the Topic Selection Oversight Panel. The technology will be appraised through the Single Technology Appraisal (STA) process. No changes to the scope are needed. |
| | PNH Support | Patients are eager to access this treatment and be relieved of symptoms caused by current unmet need/the need for blood transfusions and have an improved quality of life. They would be able to live much more independent and productive lives through being able to self-administer sub-cutaneous injections. | Thank you for your comment. No changes to the scope are needed. |

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| Wording | Apellis Pharmaceuticals | Apellis requests that the the remit is amended as follows: [redacted] Current standard therapy for PNH on the NHS is eculizumab, a C5 complement inhibitor. The Market Authorisation application with the European Medicines Agency for pegcetacoplan is focused on data from the PEGASUS Trial and the expected label is: [redacted] | Thank you for your comment. The remit has been slightly updated but remains broad to ensure that it will be compatible with the wording of the marketing authorisation when it is known. |
| | PNH Support | Under “Population” it states “People with previously treated paroxysmal nocturnal haemoglobinuria”. Does this mean people currently receiving treatment for PNH as the current wording makes it sound like people who had previously had treatment for PNH but are no longer receiving treatment. Treatment for PNH is ongoing. | Thank you for your comment. The remit has been updated to remove reference to ‘previously treated’ and therefore avoid confusion. |
| Timing Issues | Apellis Pharmaceuticals | Given the delay due to the COVID-19 lockdown, Apellis recommends submitting this appraisal to NICE with urgency. [redacted] | Thank you for your comment. No changes to the scope are needed. |
| | PNH Support | Patients are eager to access this treatment as soon as possible to improve their quality of life which is currently impacted by unmet need caused by extravascular haemolysis and the need for blood transfusions. Delivery of this treatment by sub-cutaneous injection will allow patients to live more independent and productive lives. | Thank you for your comment. No changes to the scope are needed. |

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| | | Therefore access to this drug is very important for those patients in order to improve their symptom control, quality of life and ability to fully function as a member of society, an employee, parent, carer etc. This will in turn free up NHS resource currently committed to the management and oversight of 2 weekly eculizumab infusions (the current standard of care for those needing treatment), the management of the care of these patients with unmet need including making arrangements for and delivery of blood transfusions. 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 or attending hospital for blood transfusions exposes them to an element of risk. | |
| Additional comments on the draft remit | Apellis Pharmaceuticals | As outlined above, Apellis has considerable concerns regarding the proposed referral of pegcetacoplan to the STA programme and urge NICE to reconsider this recommendation. To aid this decision, Apellis has provided an overview of eligibility based on the seven eligibility criteria for the HST programme. Apellis would be very happy to respond to further queries from NICE in relation to these points:<br><br>1. The target patient group for the technology in its anticipated licensed indication is so small and so specialised that treatment will be concentrated in very few centres in the NHS<br>o The scoping document confirms that only 239 people with PNH are currently receiving eculizumab on the NHS. It is expected that up to [redacted] of patients will be eligible to switch to pegcetacoplan<br>o PNH services (including eculizumab) are commissioned via NHS England specialised services with two centres providing treatment — King's College Hospital NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust | Thank you for your comment. The routing of this topic was considered by the Topic Selection Oversight Panel. The technology will be appraised through the Single Technology Appraisal (STA) process. No changes to the scope are needed. |

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| | | 2. The target patient group is distinct for clinical reasons<br>○ PNH is diagnosed through a highly specialised clinical technology. PNH arises due to an acquired somatic mutation of the phosphatidyl inositol glycan complementation group A (pig-a) gene in a haematopoietic stem cell which results in a haematopoietic clone deficient in a number of cell surface antigens. Primary diagnosis of PNH is confirmed by high-sensitivity flow cytometry immunophenotyping, a highly specialised technique that is performed in specialist laboratories by expert scientific staff.<br>○ The complex testing requirements and patients are managed by the National PNH Service, which comprise of only two centres within England (Leeds and King's College Hospital, London) and confirm the clinically distinct nature of eligible patients<br>○ The anticipated EMA marketing authorisation document sets out that the target patient group for pegcetacoplan is PNH patients [redacted]<br>○ Therefore, the target patient group are clinically distinct through a combination of a highly specialised clinical diagnosis of PNH, managed by the specialist National PNH Service within only two centres in England and currently treated with a C5 complement inhibitor<br>3. The condition is chronic and severely disabling<br>○ PNH is an ultra-rare life-threatening chronic blood disorder that leads to excessive breakdown of red blood cells, resulting in the release of a large amount of haemoglobin (the protein | |

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| | | found in red blood cells that carries oxygen around the body) into the urine. 40% of patients with PNH experience haemoglobinuria, thrombosis, and/or severe anaemia, all of which have a significant impact on patients' daily living. Patients are at risk of fatal disease complications, including thrombotic and haemorrhagic events, with a 10-year mortality rate of 24%–29% if left untreated. PNH is a contributing factor in the death of approximately half of sufferers.<br><br>4. [redacted]Th e technology is expected to be used exclusively in the context of a highly specialised service<br><br>o PNH treatment has been designated as a Highly Specialised Service by the NHS (2018 report) with two centres (Leeds Teaching Hospitals NHS Trust and King's College Hospital NHS Foundation Trust) providing treatment. Pegcetacoplan is expected to be used exclusively in this context. | |

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| | | 5. The technology is likely to have a very high acquisition cost<br>o Pegcetacoplan is expected to have a high acquisition cost as it addresses the limitations of existing treatment options or provides a treatment option where there is none. The price of treating a single patient is fixed as standard dosing is given twice weekly (or every 3 days). Due to relatively low patient numbers, pegcetacoplan will not have a significant impact on the NHS England budget<br>6. The technology has the potential for life-long use<br>o PNH is an ultra-rare, chronic, haemolytic disease caused by an acquired mutation in the PIG-A gene. Complications such as thrombosis and death are caused by ongoing haemolysis due to an overactivated complement system. Hence, PNH patients require chronic therapy. Pegcetacoplan is a potential therapeutic option for PNH as it selectively binds to C3 and inhibits broadly complement-mediated inflammation and cell destruction. For clinical effectiveness to be maintained for the lifetime of the patient, pegcetacoplan will need to be to be administered subcutaneously twice weekly or every 3 days indefinitely.<br>7. The need for national commissioning of the technology is significant<br>o As the treatment is to be prescribed in the few centres in which PNH is diagnosed, national commissioning and oversight will be essential. | |

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| | PNH Support | None | Thank you for your comment. No changes to the scope are needed. |

**Comment 2: the draft scope**

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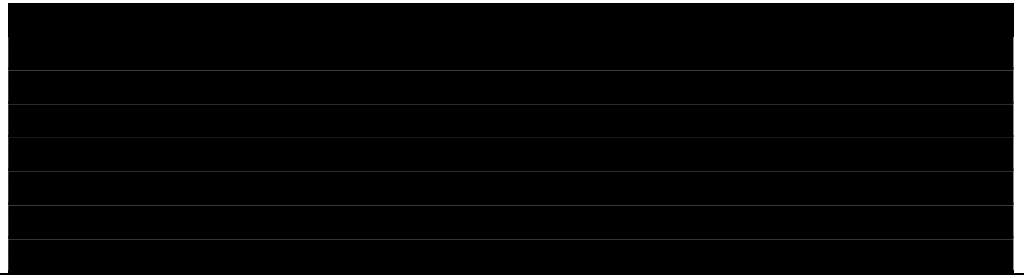
| Background information | Apellis Pharmaceuticals | Apellis would like to include in the Background Information the following evidence: patients with PNH are at risk of fatal disease complications, including thrombotic and haemorrhagic events, with a 10-year mortality rate of 24%-29%, if left untreated (de Latour et al., 2008; Fu et al., 2020; Fujioka and Asai, 1989).<br><br>Apellis would like to note that, 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<br><br>  | Thank you for your comment. The background section aims to provide a brief overview of the condition in language that is both accessible and sensitive to people with PNH. A link to the NHS England commissioning policy has been included in the scope. |

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| | | [redacted] | |
| | PNH Support | None | Thank you for your comment. No changes to the scope are needed. |
| The technology/ intervention | Apellis Pharmaceuticals | Apellis notes that the description of pegcetacoplan is not accurate and would like to add the following paragraph to the text: “Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b mediated opsonization and MAC formation, thereby controlling the mechanisms that lead to both extravascular haemolysis (EVH) and intravascular haemolysis (IVH)”<br><br>Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular haemolysis (EVH) is facilitated by C3b opsonization while intravascular haemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to EVH and IVH. These functions of pegcetacoplan underly the observed sustained reduction in complement-mediated hemolytic activity in patients with PNH. Pegcetacoplan is administered by subcutaneous injection.<br><br>The anticipated Market Authorisation from the EMA will focus only on the PEGASUS Trial, so we recommend that NICE removes references to data being available regarding comparison with best supportive care as this data will not be available at the time of this appraisal. Importantly, in the target | Thank you for your comment. The effects of pegcetacoplan on extravascular haemolysis and intravascular haemolysis will be considered by the committee during the appraisal. Reference to the PRINCE trial has been removed from the scope as it is not relevant to this indication. |

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| | | population for EMA based on the PEGASUS trial, best supportive care is not a treatment option as in this population C5 inhibitors are the standard of care.<br><br>Pegcetacoplan has been studied in one phase 3 study, the PEGASUS trial. The PEGASUS trial established the efficacy and safety of pegcetacoplan compared with eculizumab in patients with PNH [redacted]<br><br>The PRINCE trial is ongoing and will establish the efficacy and safety of pegcetacoplan in patients with PNH who had not received treatment with a complement inhibitor for ≥ 3 months before screening (naïve population). [redacted]<br><br>The draft scope should therefore refer to the anticipated Market Authorisation [redacted] | |
| | PNH Support | Do patients need to take prophylactic antibiotics whilst on this therapy? How often? What dose? How often is the subcutaneous injection needed and how long does the infusion take? Does the treatment need to be refrigerated (can this be done in a patient's household fridge?)? | Thank you for your comment. This section aims to provide a very brief overview of the technology only. No changes to the scope are needed. |
| Population | Apellis Pharmaceuticals | Apellis proposes aligning the text to the expected Market Authorisation: [redacted] | Thank you for your comment. The population has been amended to more |

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| | | No sub-groups of patients should be considered within the appraisal as the results of the PEGASUS trial show a consistent treatment effect across the population studied regardless the baseline risks. | closely reflect the trial population. |
| | PNH Support | Pegcetacoplan may be more appropriate for treating a subset of patients with PNH i.e. adults who have unmet need after treatment with eculizumab i.e. anaemia and extra-vascular haemolysis and require blood transfusions. What age group will benefit from this treatment – it is assumed this will be adults and based on the licence (once obtained). | Thank you for your comment. The population has been amended to reflect the trial population more closely. |
| Comparators | Apellis Pharmaceuticals | Apellis notes that C5 complement inhibitor is the sole comparator applicable for pegcetacoplan and asks that 'best supportive care' be removed.<br><br>The current standard therapy for PNH on the NHS is eculizumab, a C5 complement inhibitor [reference: NHS England Commissioning policy: Eculizumab in the treatment of recurrence of C3 glomerulopathy postkidney transplant (all ages) NHS England: 16054/P']. Based on the estimated population of between 650 to 900 patients, 239 are currently receiving eculizumab. It is expected that up to [redacted] of patients will be eligible for switching to pegcetacoplan.<br><br>Currently patients treated with C5 inhibitor do not have the alternative to switch to a treatment with a different mechanism of action.<br>[redacted]<br><br>[redacted] | Thank you for your comment. 'Best supportive care' has been removed as a comparator based on discussion in the workshop. |

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| | | [redacted]<br><br>Given that trial data underpinning the submission focuses on pegcetacoplan compared with eculizumab in patients with PNH [redacted] we would suggest that eculizumab could be described as the only alternative care. | |
| | PNH Support | The current standard of care currently used in the NHS for patients who need treatment is eculizumab and therefore it is an appropriate comparator. Comparators should be the standard of care (i.e. eculizumab), which standard of care has been established for 11 years, and a highly specialised service (the PNH National Service) has been built around this. “Best supportive care” is not an effective treatment for PNH patients who qualify to be treated with eculizumab. “Best supportive care” is not an appropriate comparator. | Thank you for your comment. ‘Best supportive care’ has been removed as a comparator based on discussion in the workshop. |
| Outcomes | Apellis Pharmaceuticals | Apellis appreciates that the proposed outcomes capture important health-related benefits for patients with PNH.<br><br>Apellis does, however, have concerns that the proposed outcome measures do not align with data that will be available from the PEGASUS study. PEGASUS is a prospective randomised, multicentre, open-label, active-comparator controlled study in patients with PNH who are receiving eculizumab. Patients were randomized to receive either pegcetacoplan or eculizumab. The primary objective was to establish the efficacy and safety of | Thank you for your comment. We have updated the scope to incorporate your suggestions, however, please note that we do not specify |

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| | | pegcetacoplan in patients with PNH<br>[redacted]<br>Pegcetacoplan demonstrated head-to-head superiority in mean change in hemoglobin (3.84 g/dL increase) versus a C5 inhibitor, resulting in transfusion avoidance and clinically meaningful improvements in measures of bone marrow function, anaemia, and haemolysis.<br><br>Apellis would therefore suggest that NICE reconsiders the following outcome measures within the scoping documents in light of PEGASUS trial endpoints: Break-through Haemolysis and Stabilised Hemoglobin, as these were not endpoints in the PEGASUS study.<br><br>Apellis note that in the PEGASUS trial:<br><br>Primary endpoint:<br>• Change from baseline to Week 16 haemoglobin level<br><br>Key secondary endpoints:<br>• Transfusion avoidance (yes/no), defined as the proportion of patients who do not require a transfusion during the 16-week randomised controlled period<br>• Change from baseline to Week 16 reticulocyte count<br>• Change from baseline to Week 16 lactate dehydrogenase level<br>• Change from baseline to Week 16 in the FACIT-Fatigue scale version 4<br><br>Apellis proposes the following alternative text for the section “Outcomes”:<br>“The outcome measures to be considered include:<br>• Overall survival<br>• Intravascular haemolysis (largely measured by lactate dehydrogenase [LDH] level) | measurement scales in scopes. |

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| | | • Extravascular haemolysis (largely measured by bilirubin)<br>• Transfusion avoidance<br>• Haemoglobin, normalisation and Response<br>• Thrombotic events<br>• Adverse effects of treatment<br>• Health-related quality of life" | |
| | PNH Support | Is there additional health-related quality of life data which captures relevant symptoms/issues which relate to PNH as reported by patients (in additional to the quality of life data collected by standardised measures)? | Thank you for your comment. The measures of health-related quality of life will be discussed by the committee during the appraisal. No changes to the scope are needed on this point. |
| Economic analysis | Apellis Pharmaceuticals | Apellis is broadly supportive of the overview in the scoping document regarding the economic analysis requirements.<br>In case this aids NICE's planning, the following information from the model may be helpful:<br>• A cost-utility model will be presented to compare pegcetacoplan to eculizumab from an NHS perspective over a lifetime horizon<br>• The model will use a Markov model structure [redacted] The model structure and health states were designed based on consultation with external clinical and health economics experts<br>• Patient distributions [redacted] | Thank you for your comment. No changes to the scope are needed. |

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| | | [redacted] will be estimated based on the observed data from the PEGASUS trial<br>• After the trial period, patients distribution among health states will be modelled based on transition probabilities. Transition probabilities will be estimated based on the extrapolation of the PEGASUS trial<br>• Patient utilities within the cost-utility analysis will be calculated by applying a published mapping algorithm [redacted]<br>• Resource use and costs will be taken from relevant published literature in PNH and disease analogues, if available, or clinical opinion. | |
| | PNH Support | As this therapy is delivered sub-cutaneously at home, patients (and their carers) are able to undertake employment without interruption or without having to take time off work to have intravenous infusions and are therefore able to contribute more fully to society. Self-administered injections by patients at home permit less disruption to patients' and carers' family life generally as treatment can take place in their own time, in private.<br>Patient access to treatment with Pegcetacoplan will free up NHS resource currently committed to the management and oversight of the 2 weekly eculizumab infusions and the management and oversight of those with anaemia and extravascular haemolysis who need blood transfusions.<br>There is a cost saving to the NHS by the reduced need for blood, blood transfusions and the staff associated with procuring the appropriate blood and administering the blood transfusion. | Thank you for your comment. The results of the company's economic analysis will be discussed by the committee during the appraisal. No changes to the scope are needed. |
| Equality and Diversity | Apellis Pharmaceuticals | There is no reference within the scoping document to the opportunities afforded by subcutaneous injection to support access and adherence to treatment for patients. Given that there are only two centres of excellence, | Thank you for your comment. Equality issues will be |

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| | | having the option to self-administer at home could help to address equalities by avoiding accessibility barriers such as travel.<br><br>The average age of patients in the PNH International Registry is 45 years. Hence, productivity costs are particularly important when considering PNH due to substantial time commitments required from patients and their caregivers for the intravenous administration of C5 inhibitors.<br><br>A study was conducted using a cost-consequence approach and published inputs to assess productivity loss for patients with PNH and caregivers due to C5 inhibitors treatments administered at infusion clinics in France, Germany, Italy, Russia, Spain, the UK, and the US over 2 years (Levy et al., 2019a). Total duration of therapy required for treatment was estimated by considering travel time to the infusion center, wait time in the clinic for medication preparation, infusion time for loading and maintenance doses, and recovery time (240 minutes for eculizumab and 330 minutes for ravulizumab). in the UK the lost productivity for eculizumab was $575,711 and for ravulizumab was $205,230.<br><br>Pegcetacoplan is the first at-home self-administrated subcutaneous infusion therapy in PNH, enhancing patient control in disease management and delivering potential savings by reducing the cost and burden of administration in a clinical setting. This may be of advantage during Covid-19 pandemic.<br><br>Pegcetacoplan is expected to increase productivity and societal benefit in patients with PNH. | considered during the evaluation of this topic. Please see the Equality Impact Assessment (scoping) for further information.<br><br>The innovative nature of the technology will be considered by the appraisal committee.<br><br>The NICE reference case considers outcomes from an NHS and personal social services perspective |

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| | | | rather than a societal perspective. |
| | 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 for your comment. Equality issues will be considered during the appraisal of this technology. Please see the Equality Impact Assessment (scoping) for further information. |
| Other considerations | Apellis Pharmaceuticals | None | Thank you for your comment. No changes to the scope are needed. |
| | PNH Support | None | Thank you for your comment. No changes to the scope are needed. |
| Innovation | Apellis Pharmaceuticals | Yes, Apellis considers pegecetacoplan to be innovative and a 'step-change' in the management of PNH with a potential to have a significant impact on health-related benefits and improve the way that current need is met. There are direct links with the NHS Long Term plan and the need to provide a treatment that can be delivered at home and avoid unnecessary hospital attendance and transfusion risks, including possible hospital-acquired infections. This will also release resources through avoiding a burden on | Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes |

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| | | infusion centres. There are also benefits to equity of care through accessible treatment at home and not prohibiting PNH patients' ability to access care.<br><br>On a clinical level, there are several benefits of pegcetacoplan over existing treatments. PNH is a disease of intravascular (IVH) and extravascular haemolysis (EVH)<br>• IVH is the direct destruction of red blood cells within the blood vessels, and is monitored using LDH (in full)<br>• EVH is the destruction of red blood cells outside the blood stream, such as by the liver and spleen<br>  • Elevated reticulocyte counts, and bilirubin levels are evidence of ongoing haemolysis; when LDH is controlled these elevations indicate ongoing EVH<br>  • C5 inhibitors, the only currently available treatments, have increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements<br>[redacted]<br>Pegcetacoplan demonstrated head-to-head superiority in mean change in haemoglobin levels (3.84 g/dL increase) versus a C5 inhibitor, resulting in transfusion avoidance and clinically meaningful improvements in measures of bone marrow function, anaemia, and haemolysis. | to the scope are needed. |

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| | | Pegcetacoplan enabled 85.4% of patients to be transfusion-free versus 15.4% of patients treated with a C5 inhibitor.<br><br>Pegcetacoplan provided clinically meaningful improvements in important measures of bone marrow function, anaemia, and haemolysis (absolute reticulocyte count, lactate dehydrogenase, and bilirubin levels, respectively).<br><br>Pegcetacoplan demonstrated an improvement in patient fatigue versus a C5 inhibitor (11.9-point increase) that is nearly four times the threshold for what is deemed to be clinically meaningful on the FACIT-Fatigue Scale.<br><br>Pegcetacoplan is the first self-administrated subcutaneous infusion therapy in PNH, enhancing patient control in disease management and delivering potential savings by reducing the cost and burden of administration in a clinical setting. | |
| | PNH Support | The therapy is innovative (and a step -change in the management of the condition) as it addresses current unmet need of patients on eculizumab who experience anaemia/extravascular haemolysis and may require blood transfusions. It would reduce/remove the need for blood transfusions which are time consuming and a burden on the patient and the NHS especially in a COVID 19 environment when patients wish to avoid the risk of attending hospital.<br>The fact that this therapy is able to be self -administered by a patient without the need for a healthcare professional is also innovative (and a step -change in the management of the condition) as treatment can be fitted in around work and family life which allows patients (and carers/family members) a significantly increased quality of life, increased psychological wellbeing and | Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed. |

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| | | less interruptions to patients' and carers' employment and family life generally which occur with intravenous infusions.<br>This psychological benefit is significant to patients/their carers in a variety of ways including: reduction of stress associated with experiencing possible or actual extravascular haemolysis and associated symptoms; arranging and receiving infusions and blood transfusions; stress linked to an employer's reaction to taking time off work for a 2 weekly infusion and/or to have blood transfusions. Some patients hide their condition and their need for treatment from employers in order to avoid discrimination.<br>The elimination of the need for venous access every 2 weeks (for eculizumab infusions) and for regular blood transfusions is an additional health related benefit of this therapy as damage to veins is reduced.<br>We understand that the PEGASUS trial data evidences that patients on the pegcetacoplan arm of the trial had a high significance and clinically meaningful increase in their haemoglobin and 85% of patients were transfusion independent.<br>Also, the trial did not show any difference in risk of infection between the two arms of the trial. | |
| Questions for consultation | Apellis Pharmaceuticals | **Q. To whom would pegcetacoplan be offered in the NHS?**<br>A. Pegcetacoplan is a treatment for adult patients with paroxysmal nocturnal hemoglobinuria (PNH) [redacted]<br><br>**Q. Have all relevant comparators for pegcetacoplan been included in the scope? Which treatments are considered to be established clinical practice in the NHS for PNH? How should best supportive care be defined?** | Thank you for your comments. Please see the response in the population section. |

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| | | A. Eculizumab is the current standard of care and the only applicable comparator for pegcetacoplan within the expected label. Apellis submitted a Market Authorisation application [redacted]<br><br>**Q. Do people stop treatment with eculizumab if their haemoglobin level is <10.5 g/dL? If not, does pegcetacoplan have the potential to displace eculizumab in this group?**<br>A. PNH is a rare, chronic, haemolytic disease caused by an acquired mutation in the PIG-A gene. Complications such as thrombosis and death are caused by ongoing haemolysis due to an overactivated complement system.<br>Hence, PNH patients require chronic therapy with C5 inhibitor (the only therapy available). Currently patients treated with eculizumab with haemoglobin levels <10.5 g/dL are managed by increasing the number of red blood cell transfusions and/or increasing the dose of eculizumab,the only available therapy targeting the complement system.<br><br>[redacted] | Thank you for your comments. Please see the response in the comparators section.<br><br>Thank you for your comment. No action required. |

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| | | [redacted] | |
| | | **Q Are the outcomes listed appropriate?**<br>A. No. Apellis proposes the following alternative text for the section "Outcomes":<br>"The outcome measures to be considered include:<br>• Overall Survival<br>• Intravascular Haemolysis (largely measured by lactate dehydrogenase [LDH] level)<br>• Extravascular Hemolysis (largely measured by bilirubin)<br>• Transfusion Avoidance<br>• Haemoglobin, normalization and response<br>• Thrombotic events<br>• Adverse effects of treatment<br>• Health-related quality of life" | Thank you for your comment. The outcomes section of the scope is not intended to be exhaustive. Information relating to outcomes beyond those defined in the scope can be included in the submissions. No changes to the scope are needed. |
| | | **Q Are there any subgroups of people in whom pegcetacoplan is expected to be more clinically effective and cost effective or other groups that should be examined separately?**<br>A No, pegcetacoplan demonstrated consistent efficacy in all pre-specified sub-groups analysed in the PEGAUS Study. Apellis does not expect pegcetacoplan to be more clinically effective and/or cost-effective in any subgroup of patients. | Thank you for your comment. No action required. |
| | | **Q. 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:** | |

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| | | • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pegcetacoplan will be licensed;**<br>• **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;**<br>• **could have any adverse impact on people with a particular disability or disabilities.**<br>A. There may be equality issues given the small number of centres and accessibility challenges regarding access to treatment. Pegcetacoplan with its subcutaneous home delivery could help to address these challenges.<br><br>**Q. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**<br>A. Yes, Apellis considers pegcetacoplan to be innovative and a 'step-change' in the management of PNH with a potential to have a significant impact on health-related benefits and improve the way that current need is met. There are direct links with the NHS Long Term plan and the need to provide a treatment that can be delivered at home and avoid unnecessary hospital attendance and transfusion risks, including possible hospital-acquired infections. This will also release resources through avoiding a burden on infusion centres. There are also benefits to equity of care through accessible treatment at home and not prohibiting PNH patients' ability to access care. | Thank you for your comment. Equality issues will be considered during the appraisal of this technology. Please see the Equality Impact Assessment (scoping) for further information.<br><br>Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed. |

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| | | On a clinical level, there are several benefits of pegcetacoplan over existing treatments. PNH is a disease of intravascular (IVH) and extravascular haemolysis (EVH)<br>• IVH is the direct destruction of red blood cells within the blood vessels, and is monitored using LDH (in full)<br>• EVH is the destruction of red blood cells outside the blood stream, such as by the liver and spleen<br>  • Elevated reticulocyte counts, and bilirubin levels are evidence of ongoing hemolysis; when LDH is controlled these elevations indicate ongoing EVH<br>  • C5 inhibitors, the only currently available treatments, have increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements<br>[redacted]<br>Pegcetacoplan demonstrated head-to-head superiority in haemoglobin levels (3.84 g/dL difference) versus a C5 inhibitor, resulting in transfusion avoidance and clinically meaningful improvements in measures of bone marrow function, anaemia, and haemolysis.<br><br>Pegcetacoplan enabled 85.4% of patients to be transfusion-free versus 15.4% of patients treated with a C5 inhibitor. | |

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| | | Pegcetacoplan provided clinically meaningful improvements in important measures of bone marrow function, anaemia, and haemolysis (absolute reticulocyte count, lactate dehydrogenase, and bilirubin levels, respectively).<br><br>Pegcetacoplan demonstrated an improvement in patient fatigue versus a C5 inhibitor (11.9-point increase) that is nearly four times the threshold for what is deemed to be clinically meaningful on the FACIT-Fatigue Scale.<br><br>Pegcetacoplan is the first self-administrated subcutaneous infusion therapy in PNH, enhancing patient control in disease management and delivering potential savings by reducing the cost and burden of administration in a clinical setting.<br><br>**Q. Do you consider that the use of pegcetacoplan can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br>A. This topic is under assessment. We cannot comment at this stage.<br><br>**Q To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.**<br>No specified barrier to adoption is foreseen. Current practice is based on hospital attendance for regular infusions, so a change in treatment pathway will be required to adopt pegcetacoplan as this can be administered at home by the patient or carer. The change required will reduce the resource costs, i.e.: hospital day case appointments, for the NHS and would outweigh any transformation costs required to implement these changes. From a patient and carer perspective, as pegcetacoplan is administered through a subcutaneous injection, patients will not be required to go to hospital, which is | Thank you for your comment. No action required.<br><br>Thank you for your comment. No action required. |

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| | | an advantage for them and their carers given the current COVID-19 pandemic.<br><br>**Q NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).**<br>Apellis firmly believes that pegcetacoplan meets all seven criteria and that it should be reviewed by the NICE HST process. Please see comments at the beginning of this consultation response outlining our concerns. We would be very happy to discuss this further with the NICE team and provide additional information as required. | Thank you for your comment. Please see the response in the appropriateness section. |
| | PNH Support | **To whom would pegcetacoplan be offered in the NHS?**<br>Pegcetacoplan would be offered to patients who are on eculizumab and have unmet need i.e. anaemia, extravascular haemolysis, other symptoms and may still need blood transfusions. It could also be offered to those who don't have unmet need following treatment with eculizumab inhibitors (however there is no trial data for this population).<br>**Have all relevant comparators for pegcetacoplan been included in the scope?**<br>Ravulizumab could be a comparator (although it is currently not approved for payment by NICE).<br>**How should best supportive care be defined?**<br>Best supportive care is blood transfusions, folic acid, iron and blood thinners. Eculizumab is the standard of care in the NHS for PNH since 2007. | Thank you for your comment. No action required.<br><br>Thank you for your comment. Ravulizumab has been included as a comparator in the scope subject to an ongoing NICE appraisal.<br><br>Thank you for your comment. No action required. |

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| | | **Do people stop treatment with eculizumab if their haemoglobin level is <10.5 g/dL?**<br>Patients do not stop treatment with eculizumab if their haemoglobin level <10.5 g/dL. If the complement system is not suppressed by eculizumab then haemolysis will continue and their haemoglobin will decrease together with the consequential symptoms and complications. Yes, pegcetacoplan has the potential to displace eculizumab in this group but treatment with it would not be able to be stopped for the same reason which is given above for eculizumab. | Thank you for your comment. No action required. |
| | | **Are the outcomes listed appropriate?**<br>The outcomes listed are appropriate. | Thank you for your comment. No action required. |
| | | **Are there any subgroups of people in whom pegcetacoplan is expected to be more clinically effective and cost effective or other groups that should be examined separately?**<br>Pegcetacoplan is expected to be more clinically effective for those with unmet need i.e. anaemia/extravascular haemolysis when treated with eculizumab. It could, of course, also treat patients who don't have anaemia/ extravascular haemolysis (however there are no trial data for this population). | Thank you for your comment. No action required. |
| | | **Do you consider that the use of pegcetacoplan can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br>Quality of life data relevant to PNH patients and their carers regarding the improvement of psychological wellbeing on patients/carers as a result of using pegcetacoplan (e.g. reduction of stress caused by extravascular | Thank you for your comment. The appraisal committee will consider outcomes of treatment |

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| | | haemolysis, taking time off work for intravenous infusions) and the ability for them to contribute to society more fully e.g. through work are unlikely to be included in the QALY calculation as this data is not collected.<br><br>**Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.**<br>PNH Support intends to gather data from patients/carers of patients who are being treated with pegcetacoplan to attempt to evidence the improvement in psychological wellbeing on patients/carers and the ability for them to contribute to society more fully e.g. through work. | which are important to patients and/or carers.<br><br>Thank you for your comment. NICE welcomes to the submission of evidence from patient/carer organisations or individuals. |
| Additional comments on the draft scope | Apellis Pharmaceuticals | As outlined above, Apellis has considerable concerns regarding the proposed referral of pegcetacoplan to the STA programme and urge NICE to reconsider this recommendation. To aid this decision, Apellis has provided an overview of eligibility based on the seven eligibility criteria for the HST programme. Apellis would be very happy to respond to further queries from NICE in relation to these points:<br><br>1. The target patient group for the technology in its anticipated licensed indication is so small and so specialised that treatment will be concentrated in very few centres in the NHS<br>o The scoping document confirms that only 239 people with PNH are currently receiving eculizumab on the NHS. It is expected that up to [redacted] of patients will be eligible to switch to pegcetacoplan<br>o PNH services (including eculizumab) are commissioned via NHS England specialised services with two centres providing | Thank you for your comment. The routing of this topic was considered by the Topic Selection Oversight Panel. The technology will be appraised through the Single Technology Appraisal (STA) process. No changes to the scope are needed. |

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| | | treatment — King's College Hospital NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust<br><br>2. The target patient group is distinct for clinical reasons<br><br>o PNH is diagnosed through a highly specialised clinical technology. PNH arises due to an acquired somatic mutation of the phosphatidyl inositol glycan complementation group A (pig-a) gene in a haematopoietic stem cell which results in a haematopoietic clone deficient in a number of cell surface antigens. Primary diagnosis of PNH is confirmed by high-sensitivity flow cytometry immunophenotyping, a highly specialised technique that is performed in specialist laboratories by expert scientific staff.<br>o The complex testing requirements and patients are managed by the National PNH Service, which comprise of only two centres within England (Leeds and King's College Hospital, London) and confirm the clinically distinct nature of eligible patients<br>o The anticipated EMA marketing authorisation document sets out that the target patient group for pegcetacoplan is PNH patients [redacted]<br>o Therefore, the target patient group are clinically distinct through a combination of a highly specialised clinical diagnosis of PNH, managed by the specialist National PNH Service within only two centres in England and currently treated with a C5 complement inhibitor<br><br>3. The condition is chronic and severely disabling | |

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| | | ○ PNH is an ultra-rare life-threatening chronic blood disorder that leads to excessive breakdown of red blood cells, resulting in the release of a large amount of haemoglobin (the protein found in red blood cells that carries oxygen around the body) into the urine. 40% of patients with PNH experience haemoglobinuria, thrombosis, and/or severe anaemia, all of which have a significant impact on patients' daily living. Patients are at risk of fatal disease complications, including thrombotic and haemorrhagic events, with a 10-year mortality rate of 24%–29% if left untreated. PNH is a contributing factorn the death of approximately half of sufferers.<br>○ [redacted]<br>4. The technology is expected to be used exclusively in the context of a highly specialised service<br>○ PNH treatment has been designated as a Highly Specialised Service by the NHS (2018 report) with two centres (Leeds Teaching Hospitals NHS Trust and King's College Hospital NHS | |

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| | | Foundation Trust) providing treatment. Pegcetacoplan is expected to be used exclusively in this context.<br><br>5. The technology is likely to have a very high acquisition cost<br><br>o Pegcetacoplan is expected to have a high acquisition cost as it addresses the limitations of existing treatment options or provides a treatment option where there is none. The price of treating a single patient is fixed as standard dosing is given twice weekly (or every 3 days). Due to relatively low patient numbers, pegcetacoplan will not have a significant impact on the NHS England budget<br><br>6. The technology has the potential for life-long use<br><br>o PNH is an ultra-rare, chronic, haemolytic disease caused by an acquired mutation in the PIG-A gene. Complications such as thrombosis and death are caused by ongoing haemolysis due to an overactivated complement system. Hence, PNH patients require chronic therapy. Pegcetacoplan is a potential therapeutic option for PNH as it selectively binds to C3 and inhibits broadly complement-mediated inflammation and cell destruction. For clinical effectiveness to be maintained for the lifetime of the patient, pegcetacoplan will need to be to be administered subcutaneously twice weekly or every 3 days indefinitely.<br><br>7. The need for national commissioning of the technology is significant<br><br>As the treatment is to be prescribed in the few centres in which PNH is diagnosed, national commissioning and oversight will be essential. | |

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| | PNH Support | None | Thank you for your comment. No changes to the scope are needed. |

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

Alexion Pharmaceuticals