Record of the Rare Disorders Advisory Committee Meeting held on 10 June 2025

Rare Disorders Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Rare Disorders Advisory Committee meeting; only the relevant portions of the meeting record relating to Rare Disorders Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Rare Disorders Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Table of Contents

1. Attendance

Present
Helen Evans (Chair)
Emma Glamuzina
Katherine Neas
Lynette Sadlier
Rhiannon Braund
Sarah McLean-Orsborn
Tim Stokes

Apologies
James Cleland

Observers – Invited Experts for part of meeting
Gina O'Grady
Humphrey Pullon

2. Summary of recommendations

	Pharmaceutical and Indication	Recommendation
10.4	Crovalimab for the treatment of paroxysmal nocturnal haemoglobinuria, subject to Special Authority criteria	High Priority
10.5	Eculizumab for the treatment of paroxysmal nocturnal haemoglobinuria, subject to Special Authority criteria	High Priority
10.6	Iptacopan for the treatment of paroxysmal nocturnal haemoglobinuria, subject to Special Authority criteria	High Priority
11.4	Garadacimab for the treatment of hereditary angioedema, subject to Special Authority criteria	High Priority
12.4	Pegunigalsidase alfa-iwxy (branded as Elfabrio) as enzyme replacement treatment of Fabry disease, subject to Special Authority criteria	Medium Priority
13.3	Onasemnogene abeparvovec for the treatment of spinal muscular atrophy (SMA), presymptomatic or type 1, subject to Special Authority criteria	High Priority

These recommendations are made within the context of rare disorders.

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Rare Disorders Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Rare Disorders Advisory Committee is a Specialist Advisory Committee of Pharmac. The Rare Disorders Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and

perspectives. The Rare Disorders Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Rare Disorders that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Rare Disorders that differ from the Rare Disorders Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Rare Disorders Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Rare Disorders.

4. Welcome and introduction

4.1. The Chair welcomed the Committee with a karakia.

5. Pharmac Update

5.1. The Committee noted the Pharmac Update.

5.2. The Committee noted an update about potential changes to Pharmac's rare disorders policy principles to align with the New Zealand Rare Disorders Strategy definition of rare. A consultation process is planned in the coming months before any changes are made and this will be shared with the Committee for its input.

5.3. Pharmac staff shared the updated trial approach to seek patient lived experience submissions to support the applications being considered by the Committee. Rare Disorders New Zealand facilitated these submissions from relevant patient groups. Video or written submissions were provided in advance to share with the Committee as part of its preparation for the meeting.

5.4. Pharmac staff also shared a new approach it is piloting with this meeting to broaden the clinical voices supporting these applications. For two agenda items, an Observer - Invited Expert will attend to bring their expertise in a clinical area to support the Committee's considerations. Invited Experts will be given an opportunity to share their insights following the discussion lead presentation and participate in the Committee discussion to answer any questions at the invitation of the Chair. Invited experts will not be present when the Committee votes on a recommendation. Invited Experts complete a confidentiality agreement and a declaration of interest to participate in the meeting. Pharmac staff will then consider how this approach could be developed and might support other meeting discussions in the future.

5.5. Members noted an Invited Expert was not available to support a third item, however Pharmac staff will meet with this expert separately to seek their input into the assessment of treatments for hereditary angioedema.

6. Record of Rare Disorders Specialist Advisory Committee meeting held Monday, July 8, 2024

6.1. The Committee reviewed the record of the Rare Disorders Advisory Committee meeting held on 8 July 2024 and agreed that the record be accepted.

7. Previous action points/recommendations made

7.1. The Committee noted the update provided by Pharmac staff on the status of funding applications since the last Rare Disorders Advisory Committee meeting in 2024.

7.2. Members fed back to Pharmac staff that when being provided with information regarding funding applications it would be helpful to more clearly identify which

stakeholder group submitted the application, for example a patient, clinician or a supplier.

7.3. The Committee noted that the application for alglucosidase alfa (Myozyme) for late-onset Pompe disease had been declined by Pharmac in July 2024. The Committee noted that this decision was informed by the decline recommendation received from the Rare Disorders Advisory Committee in 2018. The Committee noted that other applications for avalglucosidase alfa (Nexviazyme) for Pompe disease, including late-onset disease, would remain open.

7.3.1. The Committee noted that Pharmac staff had sought feedback on the need for the application for alglucosidase alfa (Myozyme) for infantile, juvenile and adult-onset Pompe disease to remain open, noting that decline recommendations had been received from PTAC in 2019 and 2011. The Committee considered that the application could be closed on the basis that alglucosidase alfa for infantile onset Pompe disease had been funded in 2016 and the application for alglucosidase alfa for adult onset Pompe disease had been declined in 2024.

7.3.2. Members noted that they understood that alglucosidase alfa was being discontinued by the supplier at some stage in the future, and recommended that Pharmac's focus for funding of treatments for Pompe disease should be avalglucosidase alfa (Nexviazyme).

7.4. Members noted that people with infantile onset Pompe disease had not been identified in New Zealand, so alglucosidase alfa (Myozyme) had not been required at any time since it was funded. However, it was noted that if treatment was needed then the Special Authority may need to be adjusted to allow for dosing increases. The current Special Authority limits the dose to '*no greater than 20 mg/kg every 2 weeks'* which may not be appropriate for all infants, particularly as they age. Pharmac staff acknowledged this and noted that if it was required dosing increases could be considered via the Exceptional Circumstances Framework.

7.5. The Committee noted that Pharmac had two open applications for carglumic acid, one for hyperammonaemia due to urea cycle disorders and another for organic hyperammonaemias. A member considered that the recommended access criteria for these was not clinically appropriate and should be refined. Pharmac staff agreed to follow this up further.

7.5.1. The Committee noted that carglumic acid had been funded for use in Health NZ Hospitals in 2021 for acute in-patient treatment of organic acidaemias as an alternative to haemofiltration. Members considered having access to this had been helpful, particularly for organic acidaemias.

7.6. The Committee noted that Pharmac has been in contact with the supplier about the funding of elosufase (Vimizim) for mucopolysaccharidosis (MPS) type IVA (patients under the age of 2 years) and had received updated pricing. The Committee noted that the next stage for this application is assessment by Pharmac's Health Economics Team. A member noted that there was an urgent need for this to be funded for a very small number of infants in New Zealand.

7.7. The Committee noted that nitisinone was included in Pharmac's 2024/25 Annual Tender and that Pharmac is considering funding this via the Pharmaceutical Schedule. Members considered nitisinone funding would be beneficial and would reduce the need for Exceptional Circumstances Framework applications to be completed. Members also noted a lifetime approval length would be appropriate as nitisinone is used in lifelong rare disorders.

7.8. The Committee noted that the application for miglustat for Gaucher disease had been declined by Pharmac in July 2024 on the basis that an alternative funded treatment for Gaucher disease (taliglucerase) was available.

7.9. The Committee noted that the application for miglustat for Neimann Pick Type C was proposed for decline in December 2023. The decline was not progressed in July 2024 as feedback was received from a clinician requesting ongoing consideration given new recent evidence. The Committee noted that miglustat for Neimann Pick Type C was to be discussed further at this meeting.

7.10. The Committee noted that Pharmac had sought feedback on the need for the application for SMA treatments (nusinersen and risdiplam) for people with SMA type IV (aged 19 years and over at symptom onset) to remain open, noting that a decline recommendation had been received from the Committee in 2023. The Committee was supportive that this application could be declined, and discussed whether, if new evidence was to become available, the application could be reconsidered by the Committee.

7.11. The Committee noted that the application for sapropterin for hyperphenylalaninaemia due to PKU in non-pregnant PKU patients had been declined by Pharmac in July 2024 on the basis that it has been it has been superseded by another application for sapropterin for all people with PKU, which is currently ranked on Pharmac's Options for Investment list.

7.11.1. Members discussed that generic sapropterin was available overseas, which should provide opportunities for reduced pricing and the consideration of funding in a wider range of indications. The Committee considered funding sapropterin would be lifechanging for some people with PKU as it would allow for greater liberalisation of the PKU diet.

7.11.2. Members also noted that a newer, related treatment sepiapterin had also recently become available overseas for the treatment of hyperphenylalaninaemia in people with PKU. Sepiapterin would likely allow for liberalisation of diet in a larger number of people than sapropterin.

7.12. The Committee noted that Pharmac has an open funding application for teduglutide to be funded for short bowel syndrome/intestinal failure in children, which was ranked on the Pharmac options for investment list. Members noted that there were a number of other GLP-2 analogues becoming available that may be alternatives to teduglutide and could provide options for a suitable pharmaceutical to be funded. Members noted that there is increasing evidence that bowel lengthening surgical procedures can have significant long-term complications, resulting in the repeated need for surgical resections, thus increasing the value of having pharmaceutical treatment options available. Members considered that horizon scanning of the GLP-2 analogues would be appropriate.

8. Therapeutic Group and NPPA Review

Overview of funded medicines for rare disorders and other discussion points

8.1. The Committee noted the different medicines listed on the Pharmaceutical Schedule and funded specifically for rare disorders.

8.2. The Committee noted that in February 2024 Pharmac had extended the range of funded supplements available on the Pharmaceutical Schedule for people with PKU and other inherited metabolic diseases.

8.3. The Committee noted that Pharmac was planning a procurement process that would allow suppliers interested in supplying their nutritional supplements for inherited

metabolic disorders to be considered by Pharmac for listing on the Pharmaceutical Schedule alongside currently funded supplements. This could provide people with inherited metabolic disorders with more supplement options.

8.4. The Committee discussed that there were a number of older agents for rare disorders which may not be the most effective treatments available but could provide funded options for people with rare disorders who currently have no funded treatments available. The Committee considered that where no treatments are funded then all options should be considered, however it was noted that long term continuity of supply may be an issue for some of these older pharmaceuticals.

8.5. Members discussed whether trientine could be funded as a first line treatment for Wilson disease as one of the currently funded first line treatments, D-penicillamine is often difficult to obtain due to supply issues. Pharmac staff considered that this could be reviewed, noting that the criteria for trientine for Wilson disease were implemented due to the significant cost difference between trientine and D-penicillamine. Pharmac staff noted that there had also been significant supply issues for trientine.

8.6. Members noted that there had also been significant supply issues for sodium benzoate and it could be very difficult to access at times, which was problematic for patients with hyperammonaemia.

Review of Named Patient Pharmaceutical Assessment data

8.7. Members noted that many of the requests and approvals for rare disorders through Pharmac's Exceptional Circumstances Framework were for the same pharmaceuticals eg rituximab. Pharmac staff noted that this was not unique to rare disorders and rituximab was frequently requested and funded through Pharmac's exceptional circumstances framework across many therapeutic groups.

8.7.1. Pharmac staff explained that they were planning procurement activities for a range of biologic medicines including rituximab, which could result in widening of funding to use in additional indications. Members considered this would be particularly helpful for conditions like infantile onset Pompe disease.

8.8. Members considered that the criteria for continuous glucose monitors should include hypoglycaemia disorders such as glycogen storage disorder and hyperinsulinism.

8.9. Members also considered that empagliflozin for glycogen storage disorder type 1b and other rare disorders such as Fanconi-Bickel syndrome would also be helpful but is not currently included in the NPPA outcome data provided to the Committee.

Exceptional Circumstances Framework policy review

8.10. The Committee noted a presentation from Pharmac staff providing an overview of the proposed review of Pharmac's Exceptional Circumstances framework, which includes reviewing the Special Authority waivers and the NPPA policy.

8.11. Members considered that, in their experience, there are large numbers of clinicians who do not understand the Exceptional Circumstances framework, what it is for and how to use it, which leads to inequities in access to pharmaceutical treatments.

8.12. The Committee noted that Pharmac staff plan to undertake extensive consultation on this review to ensure the issues and challenges are understood before considering solutions.

8.13. Members considered a survey might be useful to understand what the baseline is for current users of the Exceptional Circumstance's framework.

8.14. The Committee considered that through any review it would be important to understand how the Exceptional Circumstances framework relates to the funding of treatments for rare disorders.

8.15. The Committee noted that applying for applications via the NPPA application is time consuming. Members supported any efforts to make the process more patient focused and streamlined.

8.16. The Committee considered that for Pharmac to truly understand issues with the current process it would be important to consult with applicants who have had their target applications declined as well as with clinicians who do not apply.

8.17. Members considered it was also likely that regional centres are underrepresented in Exceptional Circumstances applications and should be engaged with as part of the proposed review.

8.18. Members considered it would also be helpful to engage with paediatric clinical networks.

8.19. Pharmac staff noted the review is expected to take around 9 months. They acknowledged that this review would take time and expressed their willingness to speak with any clinicians or groups about the current Exceptions framework.

Horizon scanning

8.20. Members considered that, for patients with urea cycle disorders, glycerol phenylbutyrate oral liquid (branded as Ravicti) would be very beneficial, as funding of glycerol phenylbutyrate would mean that there would be an alternative available for people who are unable to use or access sodium benzoate or sodium phenylbutyrate.

8.21. Members anticipated that Pharmac may receive funding applications for ileal bile acid transport inhibitors (IBAT) such as maralixibat, odevixibat or volixibat for patients with certain genetic liver diseases.

8.22. Members noted that gene therapies were becoming available for a range of rare disorders. Members noted that these treatments had very high upfront costs, which could not be afforded by Health NZ hospitals/services, and it was uncertain whether and how these could be funded from within Pharmac's budget.

9. Matters Arising: Miglustat for Niemann Pick Type C (NPC)

Discussion

Background

9.1. The Committee noted that the Rare Disorders Advisory Committee previously reviewed a funding application for miglustat for Niemann Pick Type C in June 2018. The Committee recommended the application be declined based on low quality evidence of benefit, and concerns regarding study design including short follow-up.

9.2. The Committee noted in 2023, during a consultation process to decline inactive funding applications, Pharmac staff were informed of new evidence for miglustat for the treatment of Niemann Pick Type C , which was provided as part of a Named Patient Pharmaceutical application (NPPA) that was approved for funding following expert clinical advice.

General

9.3. The Committee noted Niemann Pick Type C is an extremely rare disease with very limited treatment evidence in the adult population.

9.4. The Committee considered from a clinical perspective that NPPA is an appropriate pathway for this treatment, with an application likely to occur only once every three years.

9.5. The Committee noted that people requiring treatment for Niemann Pick Type C would be seen by the National Metabolic Service.

9.6. The Committee considered the funding application for miglustat for Niemann Pick Type C should be declined and this treatment continue to be accessed via the NPPA pathway.

9.7. The Committee noted this highlighted a process issue within Pharmac, and considered it was not appropriate for this funding application to proceed through the Pharmac funding pathway given the very limited patient numbers.

9.7.1. The Committee also considered a rare disorders pathway should be considered as part of the exceptional circumstances review.

10. Eculizumab, Crovalimab and Iptacopan for the treatment of paroxysmal nocturnal haemoglobinuria

10.1. Dr Humphrey Pullon, Emeritus Consultant Haematologist, Te Whatu Ora, Waikato - expert in treating paroxysmal nocturnal haemoglobinuria, attended the discussion as an Observer – Invited Expert. Dr Pullon left the meeting before the recommendation was made.

Application

10.2. The Committee reviewed the three applications for crovalimab, eculizumab and iptacopan in the treatment of paroxysmal nocturnal haemoglobinuria (PNH). These applications were received in response to Pharmac's 2024 Rare disorders call for applications. Pharmac staff considered they met Pharmac's Policy principles for rare disorders.

10.3. The Committee noted that Pharmac staff sought to understand which of these treatments may be possible first-line options for treating PNH, in addition to seeking advice on the possible treatment sequencing.

10.4. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

10.5. The Committee **recommended** that crovalimab be listed with a **high priority** for the treatment of paroxysmal nocturnal haemoglobinuria, in the context of treatments for rare disorders, subject to the following Special Authority criteria:

Initial application – (paroxysmal nocturnal haemoglobinuria)
Applications from any relevant practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. A diagnosis of paroxysmal nocturnal haemoglobinuria (PNH) confirmed by flow cytometry; and
2. A granulocyte clone size greater than 10%, and
3. Either:
   3.1. Both:
      3.1.1. Patient has previously received treatment with a complement inhibitor; and
      3.1.2. Patient has experienced previous or current clinically significant haemolysis, prior to or after commencing treatment with a complement inhibitor; or
   3.2. Both:
      3.2.1. Patient has not previously received treatment with a complement inhibitor, and
      3.2.2. Patient is experiencing clinically significant haemolysis.

Note: Evidence of clinically significant haemolysis includes haemoglobin level of less than 100 g/L,

lactate dehydrogenase levels more than 1.5 times the upper limit of normal, or a history of a thrombotic/embolic event which required anticoagulation therapy.

Renewal - From any relevant practitioner on the recommendation of a haematologist. Approvals valid for 6 months for where the treatment remains appropriate and granulocyte clone size remains greater than 10%.

10.6. The Committee **recommended** that eculizumab be listed with a **high priority** for the treatment of paroxysmal nocturnal haemoglobinuria, in the context of treatments for rare disorders, subject to the following Special Authority criteria:

Initial application – (paroxysmal nocturnal haemoglobinuria)
Applications from any relevant practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. A diagnosis of paroxysmal nocturnal haemoglobinuria (PNH) confirmed by flow cytometry; and
2. A granulocyte clone size greater than 10%, and
3. Either:
   3.1. Both:
      3.1.1. Patient has previously received treatment with a complement inhibitor; and
      3.1.2. Patient has experienced previous or current clinically significant haemolysis, prior to or after commencing treatment with a complement inhibitor; or
   3.2. Both:
      3.2.1. Patient has not previously received treatment with a complement inhibitor, and
      3.2.2. Patient is experiencing clinically significant haemolysis.

Note: Evidence of clinically significant haemolysis includes haemoglobin level of less than 100 g/L, lactate dehydrogenase levels more than 1.5 times the upper limit of normal, or a history of a thrombotic/embolic event which required anticoagulation therapy.

Renewal - From any relevant practitioner on the recommendation of a haematologist. Approvals valid for 6 months for where the treatment remains appropriate and granulocyte clone size remains greater than 10%.

10.7. The Committee **recommended** that iptacopan be listed with a **high priority** for the treatment of paroxysmal nocturnal haemoglobinuria, in the context of treatments for rare disorders, subject to the following Special Authority criteria:

Initial application – (paroxysmal nocturnal haemoglobinuria)
Applications from any relevant practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. A diagnosis of paroxysmal nocturnal haemoglobinuria (PNH) confirmed by flow cytometry; and
2. A granulocyte clone size of greater than 10%, AND
3. Either:
   3.1. Both:
      3.1.1. Patient has previously received treatment with a complement inhibitor; and
      3.1.2. Patient has experienced previous or current clinically significant haemolysis, prior to or after commencing treatment with a complement inhibitor; or
   3.2. Both:
      3.2.1. Patient has not previously received treatment with a complement inhibitor, and
      3.2.2. Patient is experiencing clinically significant haemolysis.

Note: Evidence of clinically significant haemolysis includes haemoglobin level of less than 100 g/L, lactate dehydrogenase levels more than 1.5 times the upper limit of normal, or a history of a thrombotic/embolic event which required anticoagulation therapy.

Renewal - From any relevant practitioner on the recommendation of a haematologist. Approvals valid for 6 months for where the treatment remains appropriate and granulocyte clone size remains greater than 10%.

10.8. In making these recommendations, the Committee considered:

10.8.1. The high health need of individuals living with PNH.

10.8.2. The lack of publicly funded treatment options currently available for PNH.

10.8.3. The demonstrated clinical benefit of the reviewed treatment options for PNH.

10.8.4. That Pharmac could consider listing iptacopan for the second-line treatment of paroxysmal nocturnal haemoglobinuria, if crovalimab or eculizumab were funded for this disease.

Discussion

Patient lived experience

10.9. The Committee discussed the shared video and written patient lived experience submissions. The Committee acknowledged that, in addition to reviewing the clinical data, they were deeply moved by the personal experiences shared by the individuals and whānau that are affected by PNH. The Committee recognised that sharing such stories is not easy, and members wished to express their sincere gratitude to those who took the time to contribute.

Māori impact

10.10. The Committee discussed the impact of funding therapy for the treatment of PNH on Māori health areas of focus and Māori health outcomes. The Committee noted there is limited New Zealand-specific data, and it remains unclear whether the prevalence and incidence of PNH differ for Māori compared with other ethnic groups.

Populations with high health needs

10.11. The Committee discussed the health need(s) of PNH among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs.

10.11.1. The Committee reiterated availability of New Zealand-specific data on minority populations and noted that it remains unclear whether the prevalence of PNH differs for Māori or Pacific peoples.

10.11.2. The Committee noted that individuals with PNH living in rural areas may face access challenges, particularly those requiring intravenous therapies such as eculizumab or crovalimab during the initial treatment phase. The Committee acknowledged that intravenous therapies necessitate regular infusions at appropriate healthcare facilities, and that the associated burden of travel, time commitment, and costs can be substantial.

10.11.3. The Committee noted that individuals with high health need would be anticipated to benefit most from self-administered, preferably oral therapy. Such an option would reduce the need for travel to receive treatment and would not require intensive monitoring.

10.11.4. The Committee noted that individuals with a higher body mass index (BMI) require increased dosing of crovalimab to receive therapeutic benefit.

Background

10.12. The Committee acknowledged three submissions for the indication of PNH, including two supplier applications (crovalimab and iptacopan) and one clinician application (eculizumab).

10.13. The Committee noted that an application for eculizumab for PNH was declined by Pharmac in 2013 on the basis of very high cost (refer Application Tracker). The application was considered and recommended for decline by PTAC in February 2012 and in March 2013, and was considered by the Haematology Subcommittee in

August 2012. At that time, the Haematology Subcommittee acknowledged the treatment benefits and strong supporting evidence of eculizumab in the treatment of PNH, but gave a low priority recommendation due to its high cost.

Health need

10.14. The Committee noted that PNH is an acquired, clonal haematopoietic stem cell disorder that usually presents with haemolytic anaemia and is associated with complications such as bone marrow failure and thrombosis.

10.14.1. The Committee also noted that PNH is caused by the expansion of a haematopoietic stem cell with a severe deficiency or complete absence of a glycolipid moiety (GPI) responsible for the anchorage of cell surface proteins.

10.14.2. The Committee noted that PNH results in a loss of haemoglobin through the urine due to premature destruction of erythrocytes. Haemoglobinuria is therefore particularly noticeable in the early morning due to overnight accumulation in the bladder.

10.14.3. The Committee noted symptoms of PNH tend to recur in response to physiological stressors, such as physical exertion or infection.

10.14.4. The Committee noted that PNH may be characterised by the following clinical features:

- intra-vascular haemolysis (complement mediated)
- severe thrombophilia
- renal dysfunction
- bone marrow failure (aplastic anaemia)

10.14.5. The Committee noted that, prior to the introduction of complement component 5 (C5) inhibitors and other disease-modifying therapies in international contexts, untreated PNH was associated with a poor prognosis, with thrombosis as the leading cause of mortality with a median survival of 10–20 years.

10.15. The Committee noted that New Zealand currently does not have publicly funded treatment for PNH and that some individuals are accessing therapy through compassionate access programmes provided by suppliers.

10.15.1. The Committee noted that supportive care for individuals with PNH in New Zealand includes warfarin, iron and folic acid replacement, red blood cell transfusions and corticosteroids.

10.15.2. The Committee noted that in untreated individuals, 40% experience thrombosis, and the median survival is 10–20 years from the time of diagnosis.

10.16. The Committee acknowledged the average global prevalence of PNH is estimated to be 15.9 individuals per million (Shah & Bhatt StatPearls 2023), however, the current number of in New Zealand is estimated at approximately 16 individuals. The Committee noted this figure is less than the expected number based on international prevalence rates.

10.16.1. The Committee considered the possibility of underdiagnosis of PNH in New Zealand, which may be contributing to lower-than-expected prevalence rates compared to global incidence. Members noted that this could be due to cases with small PNH clone sizes, which may present with subtle or non-specific clinical symptoms, making diagnosis more challenging.

10.16.2. The Committee however considered that the funding of a new treatment is unlikely to affect the probability of diagnosing new cases in New Zealand of what is a serious disease with clearly differentiated features.

10.17. The Committee noted impact of PNH on Health-Related Quality of Life (HRQoL), acknowledging the significant impact on individuals' ability to participate in paid work, fulfil family and community responsibilities and engage in recreational activities.

10.18. The Committee noted the significant psychological challenges experienced by individuals living with PNH, acknowledging that the chronic nature of the disease, combined with persistent fatigue and uncertainty surrounding treatment, can contribute to emotional distress.

10.19. The Committee noted the broader impacts of PNH on families, whānau, and society, acknowledging the financial strain resulting from lost income, the burden of travel for treatment, and the consumption of healthcare resources. The Committee noted that the demands of managing this disorder reduce the availability of nursing staff, infusion time and blood products for other patients.

10.20. The Committee noted that 20–25% of individuals receiving C5 therapy are reported to experience clinically significant extravascular haemolysis (csEVH) (Kulasekararaj et al. Blood Rev. 2023;59:101041; Kulasekararaj, et al. Blood Adv. 2025;pre-print). This estimate has been confirmed by New Zealand clinicians with experience treating PNH.

10.20.1. Members noted that while 20–25% of PNH patients treated with ravulizumab/ eculizumab experience csEVH, most only experience mild fatigue, which remains stable throughout the course of treatment. Members considered that only a small subset of this 20–25% (likely around 5% of the total number of individuals treated) are severely affected and require regular transfusion support due to symptomatic anaemia.

10.21. The Committee considered the treatment needs of pregnant individuals with PNH and noted that the dosing of complement inhibitors typically needs to be increased during pregnancy, primarily due to increased extravascular volume. To maintain effective control of haemolysis during pregnancy, members noted that an approximate 25% increase in dose is recommended.

Health benefit

10.22. The Committee considered the quality of evidence supporting each of the treatments under review for PNH to be high, particularly in light of the inherent challenges associated with conducting studies on rare disorders, such as limited participant numbers impeding statistical certainty.

10.23. The Committee considered the generalisability and relevance of the available evidence to the New Zealand context. The Committee noted that the evidence for key outcomes, such as improved haemoglobin levels and reduced need for transfusions, is applicable to the New Zealand PNH population.

Health benefit - crovalimab

10.24. The Committee noted that crovalimab is a terminal C5 inhibitor that is administered subcutaneously following an initial intravenous loading dose. The Committee noted crovalimab is a humanised monoclonal antibody (IgG1) that binds to C5 of the complement system, inhibiting terminal complement-mediated intravascular haemolysis.

10.25. The Committee noted two key trials, COMMODORE I (Scheinberg et al. Am J Hematol. 2024;99:1757-67) and COMMODORE II (Röth et al. Am J Hematol. 2024;99:1768-77).

10.25.1. The Committee noted that COMMODORE I did not achieve its recruitment target. As a result, the study was inherently under-powered and all efficacy endpoints had to become exploratory, with safety endpoints as the new primary objective.

10.25.2. The Committee noted that COMMODORE II was a phase III trial involving 204 participants with PNH who had not previously received C5 inhibitors. The trial compared efficacy and safety of crovalimab to eculizumab. The Committee noted comparable results between arms, with non-inferiority achieved in the two key secondary endpoints.

- The Committee noted the first primary endpoint, haemolysis control (centrally assessed lactate dehydrogenase (LDH) ≤ 1.5 x the upper limit of normal), was the same between both groups. The crovalimab arm achieved 79.3%, while the eculizumab arm achieved 79.0% (OR, 1.0 [95% CI, 0.6, 1.8]).

- The Committee noted that the second primary endpoint, transfusion avoidance, was also similar between groups. The crovalimab arm achieved 65.7% avoidance, compared to eculizumab arm which achieved 68.1% (weighted difference -2.8 [-15.7,11.1]).

Health benefit - eculizumab

10.26. The Committee noted that eculizumab is a first-in-class terminal C5 inhibitor that is administered intravenously. The Committee noted eculizumab is a humanised monoclonal antibody (IgG2/IgG4) that binds to the C5 protein and inhibits terminal complement-mediated intravascular haemolysis.

10.27. The Committee reiterated that this treatment was previously reviewed by PTAC in 2012/2013, and at that time was considered to offer clear clinical benefit supported by high-quality evidence. However, it was ultimately considered to be cost-prohibitive at the time.

10.28. The Committee noted the pivotal trial, TRIUMPH (Hillmen, et al. N Engl J Med. 2006;355(12):1233-43), had been previously considered by PTAC. The Committee noted that the study included 87 total participants, with 43 receiving eculizumab and 44 receiving placebo over a 26-week period.

10.29. The Committee noted the trial had two primary endpoints. The first was stabilisation of haemoglobin levels, which was achieved by 49% of the participants receiving eculizumab, compared with 0% in the placebo group. The second was of the number of units of packed red cells transfused, with a median of 0 units in the eculizumab group and 10 packs in the placebo group.

Health benefit - iptacopan

10.30. The Committee noted that iptacopan, an oral proximal complement inhibitor, provides control of extravascular haemolysis. The Committee noted iptacopan is a small molecule that targets factor B in the alternative pathway to control C3-mediated extravascular haemolysis and terminal complement-mediated intravascular haemolysis.

10.31. The Committee acknowledged that while eculizumab and crovalimab can only control intravascular haemolysis, iptacopan acts earlier in the complement pathway, offering a broader range of haemolysis control.

10.32. The Committee acknowledged two key trials, APPLY and APPOINT (de Latour et al. N Engl J Med 2024;390:994-1008).

10.32.1. The Committee noted APPLY was a Phase III randomised, open-label trial involving 97 individuals with PNH who had persistent anaemia despite being on a stable regimen of anti-C5 therapy for over 6 months. Participants received either iptacopan (200 mg twice daily; ie second-line therapy) or continued on with their original anti-C5 therapy (either eculizumab or ravulizumab).

10.32.2. The Committee noted in APPLY that the first primary endpoint, the proportion of participants with an increase in baseline haemoglobin of ≥ 2 g/dL without any transfusions, was significantly greater for those receiving iptacopan (82%) compared to those continuing to receive anti-C5 therapy (2%; p <0.001). Additionally, the Committee noted that the second primary endpoint, the proportion of participants with a haemoglobin level of ≥ 12 g/dL without transfusions, was also greater in the iptacopan arm (69%) compared to those continuing to receive anti-C5 therapy (2%; p <0.001).

10.32.3. The Committee noted APPOINT was a Phase III open-label, single-arm trial of 40 participants who were naïve to anti-C5 therapy (ie first-line therapy). The Committee noted for the first primary endpoint that 92% of participants receiving iptacopan experienced an increase from baseline haemoglobin of ≥ 2 g/dL without transfusions. The Committee noted for the secondary endpoint that 63% of the participants receiving iptacopan experienced a haemoglobin level of ≥12 g/dL without transfusions.

10.33. The Committee considered that the evidence supported a benefit from iptacopan in both the first- and second-line settings. The Committee considered that while there were nuances in how stabilisation and/or increase in haemoglobin was measured across the pivotal trials, overall the evidence demonstrated a significantly greater benefit for participants receiving iptacopan in comparison to either eculizumab and crovalimab, particularly in relation to experiencing transfusion independence.

10.34. Members noted that if iptacopan were to be funded only for second line use, then modified Special Authority criteria would apply.

Health benefit of PHN treatments

10.35. The Committee noted the adverse event profile of each therapy were considered reasonable and generally manageable. While minor adverse events were observed in pivotal trials, there were no significant safety concerns reported.

10.35.1. The Committee acknowledged the challenges in comparing outcomes across the key trials for eculizumab, crovalimab, and iptacopan, noting that variations in the definitions of transfusion dependence limited direct comparability.

10.36. The Committee considered overall survival benefit for individuals living with PNH, acknowledging two major sources for examining overall survival include the International PNH Registry (Terriou, et al. Eur J Haematol. 2023;111(5):796-804), in which several thousand individuals with PNH are monitored long-term, and the UK PNH cohort (Hillmen, et al. Br J Haematol. 2013;162(1):62-73), which reported that overall survival for patients treated with eculizumab was equivalent to those of age and sex-matched controls (Kelly, et al. Blood. 2011;117:6786-92).

10.37. The Committee noted the broad international consensus that significant overall survival gains are achieved with eculizumab and that similar therapies that effectively inhibit the complement pathway such as crovalimab and iptacopan would be anticipated to provide the same gains. The Committee considered these treatments prolong survival, control haemolysis, and reduce the risk of thrombosis, which is the major cause of death in untreated PNH due to major thrombotic complications.

10.38. The Committee noted that the key evidence was based on relatively short treatment durations, which may not fully capture the long-term variability and complexity of PNH management in clinical practice. Members noted that PNH clone size can vary over time, leading to fluctuations in the severity of haemolysis. These fluctuations may be triggered by external health stressors. Members considered infections such as influenza can activate the complement system, potentially overwhelming the inhibitory effects of treatments such as eculizumab and can result in breakthrough haemolysis, even in patients whose conditions were previously stable.

10.39. The Committee discussed the clinically significant risks associated with each proposed treatment. The Committee noted that inhibition of the complement pathway increases susceptibility to infections from encapsulated bacteria. The Committee discussed the differing vaccination requirements associated with complement inhibitors.

10.40. Members noted that C5 inhibitors typically require vaccination only against meningococcus. In contrast, C3 inhibitors, which act proximally in the complement pathway, require broader immunisation also against *Streptococcus pneumoniae* (pneumococcus), and *Haemophilus influenzae* type B in addition to *Neisseria meningitidis* (meningococcus).

10.41. Members noted international differences in infection prevention strategies for individuals with PNH receiving eculizumab therapy. In some jurisdictions, individuals under the age of 40 years are additionally prescribed low-dose prophylactic penicillin alongside meningococcal vaccination to further reduce the risk of serious infection.

10.42. The Committee discussed the relationship between PNH clone size and the expected benefit from treatment, noting evidence from Cannizzo et al (Cannizzo et al. Ann Hematol. 2019;98(5):1083-93). Members noted that clone size at presentation can influence treatment eligibility and clinical outcomes. The Committee noted that if using a clone size threshold of ≥50%, as recommended by the Haematology Subcommittee in 2012, then approximately 68% of individuals with PNH would be eligible for treatment. If the threshold is lowered to ≥10%, eligibility increases to around 82%. Members considered the difference in patient numbers between the two thresholds to not be substantial. Members also noted that larger clone sizes are generally associated with more pronounced red cell haemolysis, reinforcing the clinical relevance of clone size in guiding treatment decisions.

10.43. The Committee noted that in most international jurisdictions where eculizumab is funded, a PNH clone size of ≥10% is commonly used as the threshold for treatment eligibility. Members note that this approach is supported by New Zealand clinicians currently managing PNH as those with a clone size between 10-50% were still at risk of thrombotic events.

10.44. The Committee was informed of exceptional cases reported in the United Kingdom in 2016, where approximately 2–3% of patients experienced a reduction in PNH clone size to below 10% and subsequently discontinued eculizumab therapy (Sahin, et al. J Haematology. 2014;3(2):50-3). Members considered while such changes in disease behaviour are rare, they underscore the importance of close and ongoing monitoring to ensure appropriate treatment decisions are made. The Committee considered that the six-monthly criteria renewal should be completed by a specialist, with clone size checked during the same appointment to ensure consistent monitoring.

10.45. The Committee considered it would be reasonable for Pharmac to undertake a competitive procurement activity which could result in a single complement inhibitor being funded for PNH in New Zealand.

Suitability

10.46. The Committee noted the differences in suitability between each considered PNH therapy. Eculizumab is administered intravenously every two weeks, with an infusion time of up to 45-minutes. Crovalimab requires an initial intravenous dose, which can be up to 90-minute duration, followed by subcutaneous administration weekly for 4 weeks, and then subcutaneous administration every 4 weeks (with dosing based on under or over 100kg in body weight). Iptacopan is the only oral therapy considered, with twice-daily dosing.

10.47. The Committee acknowledged that health-related quality of life (HRQoL) is improved depending on the method of administration, with subcutaneous administration being more beneficial than intravenous. Additionally, while oral administration also enhances HRQoL, the Committee considered the improvement is not as significant as the leap from intravenous to subcutaneous.

10.48. The Committee noted commentary in the COMMODORE II trial publication (Röth et al. 2024) highlighting how, despite the availability of effective and well-tolerated treatments, patients with PNH consider poor quality of life related to treatment burden among the key issues they face in living with the disease. The study noted that treatments that require frequent intravenous infusions or regular healthcare facility appointments can contribute to this burden. The Committee noted that clinical evidence indicates that patients had additional HRQoL benefits from receiving treatments subcutaneously that are independent of the effects of the treatment itself.

Cost and savings

10.49. The Committee considered that all proposed treatments would likely require less ongoing monitoring and primary care input than the current best supportive care.

Funding criteria

10.50. The Committee reviewed the proposed Special Authority criteria for first-line use of crovalimab, eculizumab, and iptacopan.

10.50.1. The Committee noted that including the word “confirmed” would provide greater diagnostic accuracy.

10.50.2. The Committee considered it essential to continue monitoring granulocyte clone size after initiating treatment, and considered that approval of renewal applications should be contingent upon confirming granulocyte clone size remains at >10%.

10.50.3. The Committee considered the severity of PNH and the need for ongoing monitoring of thrombotic risk, extravascular haemolysis, infusion requirements, and end-organ complications. Members noted ongoing monitoring was manageable from rural areas. The Committee noted that individuals with PNH require regular monitoring by a haematologist and considered that six-monthly approval periods are appropriate.

10.50.4. The Committee considered it appropriate to expand the definition of clinically significant haemolysis to include individuals with a history of major thrombotic events requiring anticoagulation therapy. Additionally, the Committee noted that in New Zealand, haemoglobin levels are typically reported in g/L, rather than g/dL as is common internationally.

10.51. The Committee considered that if iptacopan were funded as a second-line treatment (only), it would be appropriate to restrict its use to individuals experiencing severe extravascular haemolysis. The Committee acknowledged the definition as patients with an ongoing requirement for blood transfusions despite receiving C5 inhibitor therapy. Based on New Zealand clinician opinion, this is expected to be approximately 5% of all PNH patients.

10.51.1. The Committee considered that the criterion regarding persistent haemolytic anaemia despite treatment with a C5 inhibitor was too broad for targeting second-line treatment, as all patients are likely to exhibit some level of persistent haemolytic anaemia. The Committee proposed the criterion specify a persistent transfusion requirement despite treatment with a C5 complement inhibitor. For clarity, the Committee defined a persistent transfusion requirement as the need for at least two units of red blood cells within any three-month period.

Summary for assessment

10.52. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for crovalimab, eculizumab and/or iptacopan if they were to be funded in New Zealand for PNH. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

<table>
<tr><td>Population</td><td colspan="5">Individuals with paroxysmal nocturnal haemoglobinuria (PNH) with a clone size greater than 10% and clinically significant haemolysis, defined as, haemoglobin levels of less than 100 g/L, lactate dehydrogenase levels more than 1.5 times the upper limit of normal, or a history of a thrombotic/embolic event which required anticoagulation therapy.</td></tr>
<tr><td>Intervention</td><td colspan="5"><table>
<tr><td></td><td>eculizumab</td><td colspan="2">crovalimab</td><td>iptacopan</td></tr>
<tr><td rowspan="2">Loading dose</td><td rowspan="2">600mg weekly for four weeks, 900mg week five intravenously</td><td>Under 100kgs</td><td>100kgs+</td><td rowspan="3">200mg tablets twice daily</td></tr>
<tr><td>1000mg day one intravenously, 340mg days 2, 8, 15, 22 subcutaneously</td><td>1500mg day one intravenously 340mg days 2, 8, 15, 22 subcutaneously</td></tr>
<tr><td>Maintenance dose</td><td>900mg every two weeks intravenously</td><td>680mg day one of every 28-day cycle subcutaneously</td><td>1020mg day one of every 28-day cycle subcutaneously</td></tr>
</table></td></tr>
<tr><td>Comparator(s) (NZ context)</td><td colspan="5">Best supportive care</td></tr>
<tr><td>Outcome(s)</td><td colspan="5">Haemolysis and thrombosis control
Increased rates of haemolysis control and stabilised haemoglobin levels with eculizumab compared to placebo in the TRIUMPH trial.
Crovalimab was non-inferior to eculizumab for haemolysis control in the COMMODORE 2 trial.
Decreased rates of breakthrough haemolysis in treatment naïve patients with iptacopan in the Appoint trial compared to eculizumab in the TRIUMPH trial
Decreased rates of breakthrough haemolysis with iptacopan compared to continued use of a C5 inhibitor in patients with residual anaemia after treatment with a C5 inhibitor in the APPLY trial.
Reduced risk of venous and arterial thrombosis associated with eculizumab, crovalimab or iptacopan.
Blood transfusions</td></tr>
</table>

	• Reduced of transfusion requirements with eculizumab, compared to placebo, based on the TRIUMPH trial. • Non-inferior rates of transfusion reduction in crovalimab compared to eculizumab in COMMODORE 2 trial. • Reduced transfusion requirements in treatment naïve patients with iptacopan in the APPOINT trial compared to eculizumab in the TRIUMPH trial (indirect comparison). • Reduced transfusion requirements with iptacopan compared to continued use of a C5 inhibitor in patients with residual anaemia after treatment with a C5 inhibitor in the APPLY trial. *Quality of life* • Improved health-related quality of life and reduced symptoms with eculizumab compared to no treatment, based on Hillmen et al. 2006. • Similar improvement in quality of life assumed for other treatments given the correlation between quality-of-life improvement and transfusion avoidance (Ito et al. Blood 2024;145:127-40). • Possible additional QOL gains with the use of subcutaneous administration (ie. crovalimab). *Improved overall survival* • Likely improved overall survival, based on observational cohort data for eculizumab (Terriou et al. 2023, Loschi et al. 2016). Similar overall survival assumed for other treatments, given absence of evidence to the contrary.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

11. Garadacimab for hereditary angioedema (HAE)

Application

11.1. The Committee reviewed the application for garadacimab in the treatment of for hereditary angioedema (HAE). This application was received in response to Pharmac's 2024 Rare disorders call for applications. Pharmac staff considered it met Pharmac's Policy principles for rare disorders.

11.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

11.3. The Committee **recommended** that garadacimab be funded for the treatment of hereditary angioedema, with **high priority** within the context of treatments for rare disorders, and subject to the following pending Special Authority criteria, with uncertainties underlined (see item 12.7):

Initial application - (hereditary angioedema) from a clinical immunologist or specialist allergist, or any relevant practitioner under the recommendation of a clinical immunologist or specialist allergist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Patient has chronic hereditary angioedema (HAE) type 1 or type 2; and
2. Either:
   2.1. Patient is receiving routine prophylaxis for HAE with a C1 esterase inhibitor at the time of application; or
   2.2. Patient has an Angioedema Control Test score of ≤10; or
   2.3. Patient has experienced at least [three or twelve] treated acute HAE attacks within the previous [three months or six months], defined as those of a severity necessitating immediate medical intervention with either icatibant or C1-esterase inhibitor concentrate; and
3. Treatment is not in combination with routine C1-esterase inhibitor concentrate.

Renewal - from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Patient has experienced, and continues to experience, an adequate response to treatment, defined as a reduction in the baseline number of attacks of a severity necessitating medical intervention with either icatibant or C1-esterase inhibitor; and
2. Treatment is not in combination with a C1-esterase inhibitor concentrate.

11.4. In making this recommendation, the Committee considered:

11.4.1. that people with uncontrolled HAE have a high and unmet health need due to unpredictable, painful, and potentially life-threatening attacks.

11.4.2. there are no funded medicines on the pharmaceutical schedule to prevent HAE attacks, leaving patients reliant on reactive on-demand treatments.

11.4.3. that garadacimab provides a meaningful reduction in monthly HAE attacks with a favourable safety profile, and many people remain attack-free while on treatment.

11.5. The Committee noted an intended Observer – Invited Expert was not available to join the discussion and recommended that Pharmac seek further advice from a relevant specialist on the underlined details in the pending Special Authority criteria listed above, specifically:

11.5.1. whether the Angioedema Control Test (AECT) is used in routine clinical practice in NZ, and if it should be included in the criteria to capture individuals with HAE who experience severe but relatively infrequent attacks (criterion 2.2).

11.5.2. whether the requisite HAE attack rate should be at least 3 attacks in 3 months, or 12 attacks in six months (criterion 2.3).

11.6. Upon refining these criteria, the Committee considered that the Special Authority criteria for lanadelumab should be updated to match garadacimab.

11.7. The Committee **recommended** Pharmac seek further advice from a relevant practitioner or the New Zealand Blood Service (NZBS) regarding whether increased use of subcutaneous C1-INH (Berinert-SC) instead of intravenous C1-INH (Berinert) is anticipated in New Zealand.

Discussion

Patient lived experience

11.8. The Committee discussed the shared video and written patient lived experience submissions from HAE Australasia. Refer to Health Need section for more information (12.18).

Māori impact

11.9. The Committee discussed the impact of funding garadacimab for the treatment of hereditary angioedema on Māori health areas of focus and Māori health outcomes. The Committee noted that HAE is not identified as a Hauora Arotahi (Pharmac Māori Health Areas of Focus). The Committee considered that although there is no evidence to suggest HAE is more prevalent in Māori, this does not exclude the possibility that Māori with HAE experience inequitable access to specialist services and/or inequitable health outcomes.

Populations with high health needs

11.10. The Committee discussed the health need(s) of HAE among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding garadacimab and did not identify any known issues for why these populations would not benefit from treatment with garadacimab, but noted the lack of evidence does not discount the possible presence of these inequities.

Background

11.11. The Committee noted that while icatibant is listed on the Pharmaceutical Schedule for the on-demand treatment of acute HAE attacks, there are no medicines listed for the routine prevention of HAE attacks. However, some people with severe HAE receive funded lanadelumab via Pharmac's Exceptional Circumstances framework and others received funded C1 esterase inhibitor (Berinert) from the New Zealand Blood Service.

11.12. The Committee noted its prior review of an application for lanadelumab for the routine prevention of recurrent HAE at its meeting in May 2024. The funding proposal was recommended with high priority, in the context of treatments for rare disorders, and subject to Special Authority criteria. The Committee considered this proposal to be targeting the same population as the garadacimab proposal, although the applications presented slightly different eligibility criteria.

11.13. The Committee noted horizon scanning data for HAE prophylactics included in the lanadelumab submission in 2024 and considered the field of HAE prophylaxis to be rapidly changing, noting several therapeutics in development including STAR-0125, Deucrictibant, NTLA-2002, and BioMarin-AAV-Gene Therapy.

11.14. The Committee was made aware of the findings of Anderson et al. Clin Transl Allergy. 2022;18:e12092, which indicated that over the past 15 years, the most frequently used HAE prophylactic treatment in the US transitioned from predominantly danazol in 2010 to being C1-INH blood products in 2013 and 2019. In 2019, lanadelumab accounted for 21% of the medications reported as most frequently used, and the Committee considered this proportion likely to have grown significantly since then.

Health need

11.15. The Committee considered that the health needs of those living with HAE to be comprehensively detailed in the record of lanadelumab's consideration at its May 2024 meeting.

11.16. The Committee noted having reviewed two video submissions from people living with HAE, and reviewed a letter written in support of the garadacimab application from HAE Australasia. The Committee considered these submissions to be deeply impactful, and their perspectives and insights were used for informing their review of the application, acknowledging specifically,

11.16.1. the debilitating and severe nature of HAE attacks, including attacks of the face requiring hospitalisation, and excruciatingly painful abdominal attacks, which coincide with fainting, vomiting, extreme thirst, and functionally prevent people from undertaking their usual daily living activities for a few days following a single attack.

11.16.2. impacts on quality of life; children missing school and social activities, adults struggling to maintain employment and engage in daily life, families facing ongoing stress, limited travel options, and social isolation.

11.16.3. experiencing transformative and life changing impacts with taking garadacimab, including getting to enjoy a full and normal life without attacks or the fear of attacks.

11.17. The Committee considered those living with HAE face a lifelong risk of unpredictable HAE attacks, which are potentially life-threatening episodes of submucosal or subcutaneous swelling, commonly affecting the larynx, abdomen and peripheries. The Committee noted these attacks significantly affect the quality of life for people living with HAE, as well as that of their family, whānau, and carers. In addition to the associated health risks, HAE attacks affecting the face and peripheries may be disfiguring, those affecting the abdomen can be painfully disabling, and those affecting the larynx can cause suffocation and lead to death.

11.18. The Committee noted that type 1 HAE is caused by a deficiency in C1 esterase inhibitor (C1-INH) protein levels while type 2 HAE is caused a dysfunction of C1-INH.

11.19. The Committee noted the findings of a 2019 national audit of HAE (Lindsay et al. Intern Med J. 2022;52:2124-9), which identified 51 New Zealanders who had been diagnosed with HAE. Of the 38 people who participated in the survey, 33 of were New Zealand European, three were Māori, and two identified as other.

11.20. The Committee considered the likely closest estimate of HAE prevalence to be 1 in 50,000 (Fisch et al. Int Arch Allergy Immunol. 2025;186:802-810).

11.21. The Committee noted Lindsey et al. 2022 reported that people living with HAE in New Zealand experienced five attacks per year (median), although rates ranged from 1-90 attacks per year. During the 12-month data collection period, 14 out of 37 participants reported experiencing an average of one or more attacks per month, while nine out of 37 participants reported an average of two or more attacks per month.

11.22. The Committee noted that in New Zealand, a small proportion of people receive preventative treatments, either subcutaneous Berinert (an C1-INH concentrate blood product funded by the NZBS), oral anabolic steroids (stanozolol), or lanadelumab, both funded through Pharmac's Exceptional Circumstances Framework. When HAE attacks occur, they are predominately managed with icatibant and/or intravenous Berinert on demand. The Committee considered this approach to be suboptimal and identified the absence of a funded next-generation preventative treatment for HAE attacks as an unmet health need for those living with HAE.

Health benefit

11.23. The Committee noted that garadacimab is not approved by Medsafe.

11.24. The Committee noted the VANGUARD trial (Craig et al. Lancet 2023;401:1079-90) as pivotal evidence for this application. VANGUARD was a randomised, double blind, placebo-controlled Phase III study that recruited individuals with poorly controlled HAE, experiencing at least three HAE attacks over three months. The Committee noted that the mean number of attacks observed during the three months before screening was 8.9 attacks (95% CI: 7.1-10.6), equating to a monthly attack rate of

nearly three attacks per month. Over the six-month study, 39 individuals received monthly garadacimab, while 26 people were given placebo.

11.24.1. The Committee noted that treatment with garadacimab was associated with significantly reduced mean monthly attack rates (0.27 attacks per month, 95%CI: 0.05-0.49) compared to those treated with placebo (2.01 attacks per month, 95%CI: 1.44-2.57; p<0.001). The proportion of patients who were attack free over the 6-month study period was also significantly greater in those receiving garadacimab (62%) compared to those receiving placebo (0%; p<0.0001).

11.24.2. The Committee noted that treatment with garadacimab was associated with significantly reduced HAE attacks that required on-demand treatment (0.23 attacks per month: 95%CI 0.02-2.46) compared to those who received placebo (1.86 attacks per month, 95%CI: 1.26-2.46; p<0.0001).

11.24.3. The Committee noted that the mean change from baseline in the Angioedema-Quality of Life (Ae-QOL) patient reported outcome measure was significantly better for those receiving garadacimab (total score: -27.1) than those receiving placebo (total score: -3.4). The Committee noted that the reported minimal clinically important difference of the AE-QoL total score was a change of six points (Weller et al. Allergy. 2016;71:1203-9).

11.24.4. The Committee considered the trial population too small to comprehensively document the risk profile associated with taking garadacimab, particularly for rare adverse events. The Committee noted that the proportion of individuals presenting with treatment emergent adverse events (TEAE) was comparable between those receiving garadacimab (64%) and those receiving placebo (60%). The Committee noted that most TEAEs assessed were not treatment related and were of mild or moderate severity.

11.24.5. Members considered VANGUARD to be a well conducted trial with clear evidence of a clinical benefit and no evidence of adverse safety.

11.25. The Committee noted the ongoing VANGUARD open label extension (OLE) (Reshef et al. Allergy. 2025;80:545-56) as additional key evidence. In addition to new enrolments, the VANGUARD OLE included individuals who rolled over from VANGUARD as well as a separate Phase II study of garadacimab, for a total of 161 individuals receiving treatment. The Committee noted the most recent published interim analysis (Reshef et al. 2025), with a median time of garadacimab exposure of 13.8 months, as well as unpublished data provided in the applicant's submissions, which contained the most recent data out to 42 months.

11.25.1. The Committee considered that both the published OLE and unpublished 42-month data indicate that garadacimab rapidly reduced the number of monthly HAE attacks and maintained its therapeutic benefit for the duration of the study period. Members noted that the mean attack rate was decreased by 95% from the study run-in period, and 60% of patients were attack-free (Reshef et al. 2025).

11.25.2. The Committee noted that most TEAEs were of mild or moderate severity and considered the evidence indicated garadacimab is well tolerated. No serious adverse events were found to be related to garadacimab. Garadacimab related TEAEs were most commonly injection site reactions (ISR). Members noted that one participant discontinued treatment from a moderate ISR.

11.26. The Committee noted the indirect-treatment comparison (ITC) submitted by the supplier and considered the absence of independent peer-reviewed ITC a limitation for the comparison of lanadelumab and garadacimab. The ITC included a comparison

of monthly attack rates between garadacimab, lanadelumab (both four weekly and two weekly), and C1-INH blood products (among other HAE prophylaxis).

11.26.1. Members noted that the applicant used the ITC to suggest that garadacimab likely has favourable efficacy compared to lanadelumab (four weekly) and non-inferior efficacy compared to lanadelumab (two weekly), while having a non-inferior safety profile to both lanadelumab dosing regimens. The Committee considered the validity of this to be uncertain, given the inherent limitations of indirect comparisons. Members noted the applicant further indicated that garadacimab improved efficacy and comparable safety to subcutaneous C1-INH therapy.

11.26.2. The Committee noted that with the evidence available (the applicant's ITC, and key trials for lanadelumab and garadacimab), it was reasonable to consider garadacimab non-inferior to lanadelumab in terms of efficacy. Members considered there was uncertainty on the relative adverse risk profile between these two medicines. Members expressed caution, given the lack of an independent peer-reviewed ITC or a direct treatment comparison.

11.27. The Committee noted the applicant's inclusion of limited survey data from Australian clinicians, as well as recent international audits, which suggested that many people in practice could not extend from lanadelumab (two weekly) to lanadelumab (four weekly).

11.27.1. The Committee was made aware of a US data claims study (Princic et al. Drugs Real World Outcomes. 2025;12:17-24), reporting that of 54 identified people who had been receiving lanadelumab for ≥ 18 months, 25 (46%) were able to reduce the administration frequency from two weekly to four weekly. Members noted that those who reduced their administration frequency experienced fewer hereditary angioedema symptoms both prior to initiating lanadelumab (baseline) and during months 0–6, compared to those who did not, suggesting that people with lower disease activity were more likely to reduce their dosing frequency.

11.27.2. The Committee was also made aware of the findings of INTEGRATED, a European observational study (Magerl et al. J Allergy Immunol Pract. 2025;13:378-87), reporting that 72.7% of people had evidence of at least one increase in lanadelumab dosing interval. Further at 36 months, the most common dosing interval was four weekly (44.4%) while roughly half that remained on two weekly (26.7%). Members noted that people were also reported to be using other intervals, ranging between every two weeks to every eight weeks.

11.27.3. Overall, members considered there was sufficient evidence that many people can transition to an extended lanadelumab dosing regimen, but that there were people who would remain on two weekly.

11.28. The Committee considered that the reduction in monthly attack rates and reduced need for on-demand therapy would result in people with HAE spending less time in hospitals for severe attacks.

Suitability

11.29. The Committee noted that garadacimab is administered monthly via a subcutaneous injection with a pre-filled pen (auto-injector), with a retractable needle. The Committee considered that in comparison to lanadelumab's pre-filled syringe presentation, the pre-filled pen presents some minor suitability advantages including ease of use, particularly for those people who are less dextrous, monthly dosing for the entire population, as well as extended shelf life when stored at ≤25 °C (two months vs 14

days). The Committee considered that people with HAE would likely prefer garadacimab's presentation given a choice, but that funding either treatment would be appropriate and would address the unmet health need.

11.30. The Committee considered that treatment with garadacimab (and lanadelumab) presents significant suitability advantages compared to managing HAE attacks with on demand treatment only.

International Funding Recommendations

11.31. The Committee noted that in Australia the Pharmaceutical Benefits Advisory Committee (PBAC) had recommended garadacimab be funded, with a restriction to those with 12 or more attacks within a six-month period. This recommendation was noted to have been made in the context that listing garadacimab would be cost-effective if it was priced the same as lanadelumab, which Australia funds.

Cost and savings

11.32. The Committee considered it would be appropriate to undertake a competitive procurement process to fund a single monoclonal antibody for the treatment of HAE which could result in the funding of either garadacimab or lanadelumab, or another comparable treatment.

11.33. The Committee considered there could be savings to the health sector from garadacimab, from reduced preventative Berinert use and from reduced need for treatment for attacks (reduced hospitalisation costs, icatibant and Berinert).

11.34. The Committee noted the cost difference between intravenous C1-INH (Berinert) and subcutaneous C1-INH (Berinert-SC). It recommended Pharmac seek advice from the NZBS or a relevant specialist on the proportional use of these two agents currently and whether a shift in proportion or total C1-INH use is anticipated in New Zealand.

Funding criteria

11.35. The Committee noted that the supplier's proposed funding criterion regarding the requisite monthly attack rate (one attack per month) differed from the more restrictive attack rate the Committee had recommended for lanadelumab (12 attacks per six months = two attacks per month). Members noted that the restriction recommended by the PBAC was 12 attacks or more within a 6-month period. The Committee noted that while the eligibility criteria from VANGUARD specified a requisite attack rate of one attack per month, the population who received garadacimab was reported to have a mean attack rate of 8.6 attacks over the three months (95%CI 6.3-10.9), ie triple the requisite rate. The Committee noted that using the one attack per month criterion threshold would increase the number of people eligible for treatment. The Committee recommended that Pharmac seek advice from a relevant expert on the requisite attack rate appropriate for the New Zealand context (three in three months, or 12 in six months).

11.36. The Committee considered that treatment with garadacimab may provide a benefit for individuals who experience one attack per month (not more), as severe but relatively infrequent attacks still present a significant disease burden. Members noted that in these scenarios, use of the ACET patient reported outcome measure may be required to determine if the patient was benefiting from treatment. The Committee recommended that Pharmac reach out to NZ clinicians who treat people with HAE, to enquire about the utility and routine use of the AECT patient reported measure tool, and regarding its appropriateness within the Special Authority criteria.

11.37. The Committee considered it was appropriate for its recommended eligibility criteria for garadacimab and lanadelumab to be the same, as both medicines are intended for the same population. The Committee also considered that changes made to the

Special Authority criteria in response to future advice may be used to update details in the population section of the below PICO table (such as the monthly attack rate).

Summary for assessment

11.38. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for garadacimab if it were to be funded in New Zealand for HAE. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with hereditary angioedema (HAE) Type I or II who have poorly controlled angioedema, defined as those who • experience 3 or more HAE attacks within a 3-month period, OR • have an Angioedema Control Test (AECT) score of ≤10, OR • are already receiving prophylactic therapy with a C1 esterase inhibitor concentrate blood product.
Intervention	Garadacimab, subcutaneous injection. Product is a 200 mg prefilled syringe (auto-injector pen); after a 400 mg loading dose, 200 mg is administered monthly. Treatment is lifelong if appropriate.
Comparators (NZ context)	Prophylaxis: either no prophylactic treatment (on-demand treatment only), or C1-INH blood products (Berinert). Estimated 89/11% split. On-demand treatment of attacks: icatibant and/or Berinert
Outcomes	Reduction in angioedema attack rates, with associated reductions in attack-induced pain, disability, mental health impacts, and death. Key evidence indicates a reduction of attacks of more than 90% compared with no prophylaxis.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

12. Pegunigalsidase alfa-iwxj for Fabry disease

Application

12.1. The Committee reviewed the application for pegunigalsidase alfa-iwxy as enzyme replacement treatment of Fabry disease. This application was received in response to Pharmac's 2024 Rare disorders call for applications. Pharmac staff considered it met Pharmac's Policy principles for rare disorders.

12.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

12.3. The Committee **recommended** that pegunigalsidase alfa-iwxy (branded as Elfabrio), as enzyme replacement treatment of Fabry disease, be funded with a **medium priority** within the context of treatments for rare disorders, subject to the following Special Authority criteria (same criteria previously recommended for agalsidase alfa and agalsidase beta):

Special Authority for Subsidy
Initial application – from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

Both:

1. The person has been diagnosed with Fabry disease confirmed by demonstration of deficiency of alpha-galactosidase enzyme activity in blood or white cells and/or the presence of a pathogenic GLA variant known to result in deficiency of alpha-galactosidase enzyme activity; and
2. Any of the following:
    - 2.1. Person has renal disease as defined as:
        - 2.1.1. abnormal albumin (>20 ug/min from at least 2 measurements more than 24 hours apart; male only); and/or
        - 2.1.2. albumin: creatine ratio higher than the upper limit of normal (2 separate measurement, 24 hours apart; males only); proteinuria (>150 mg/hours in male and >300 mg/24 hours in females with clinical evidence of progression); and/or
        - 2.1.3. disease caused by long-term glycosphingolipids deposition in the kidneys; or
    - 2.2. Person has Fabry-related cardiac disease: left ventricular hypertrophy (determined by MRI or ECG) and/or arrhythmia or conduction defect; or
    - 2.3. Person has ischaemic vascular disease: determined on objective measures; or
    - 2.4. Person has uncontrolled chronic pain despite use of appropriate doses of analgesic/antiepileptic medications; or
    - 2.5. Person has uncontrolled Fabry related gastrointestinal symptoms as defined by the gastrointestinal symptom rating scale (GSRS) despite the use of other therapeutics; or
    - 2.6. Person has significant health-related quality of life limitations due to Fabry disease as assessed by a metabolic medicine specialist.

Renewal –from any relevant practitioner specialist. Approvals valid for 12 months for applications meeting the following criterion:

1. The treatment remains appropriate, and the person is benefitting from treatment.

12.4. In making this recommendation, the Committee:

12.4.1. Noted the high need of people with Fabry disease, their families, whānau and wider community as highlighted in the current and previous patient lived experience submissions and in previous clinical advice records, especially in the NZ context without funded Fabry disease treatments

12.4.2. Noted the previous priority recommendations for agalsidase alfa (AGA-A) and agalsidase beta (AGA-B) for Fabry disease and the Committee's May 2024 consideration that AGA-A and AGA-B are similar and could be considered interchangeable in the treatment of Fabry disease

12.4.3. Considered that the key difference between the recommendation for pegunigalsidase alfa-iwxy (PEG-A) and those for AGA-A and AGA-B (taking into account the most recent view on their interchangeability) was that the evidence base for PEG-A is not as mature or broad

Discussion

Patient lived experience

12.5. The Committee acknowledged the written submission made on behalf of the New Zealand (NZ) Fabry community of patients, families and caregivers who live with daily challenges of this rare, progressive and life-limiting disease. The Committee read and considered this personal information, noting the impact that Fabry disease (especially whilst untreated) has in NZ on individuals, families, generations and the health system. The Committee thanked the Fabry community for their time, effort and courage in sharing their lived experience to help inform its consideration of this new funding application for Fabry disease.

12.6. The Committee acknowledged that this reflected a request for the same rights to health for people with Fabry disease in NZ as those in comparable countries where Fabry disease treatments are funded. The Committee noted that the letter described that there would be a significant gain in life with Fabry treatment and reductions in hospitalisation, severe pain and disability, and prevention of early death. The Committee acknowledged that the unmet health need of people with Fabry disease in NZ is great and has been for decades.

12.7. The Committee noted the inequities within families in access to Fabry treatment in NZ as highlighted in the submission, with some having access to Fabry treatment via compassionate access programmes following clinical trial participation whilst others in the same family did not have funded treatment access. The Committee agreed with the NZ Fabry community's comment that many people with Fabry disease in NZ would receive benefit from a funded Fabry disease-specific treatment.

12.8. The Committee noted that this submission spoke to many of the impacts experienced by those who provided lived experience input into the 2024 consideration of Fabry disease. The Committee noted it also aligned with the August 2024 correspondence from Fabry NZ outlining its hopes to prioritise funding for Fabry medications, and the need for discussion to improve pathways for rare disorder medicine in light of the Aotearoa New Zealand Rare Disorders Strategy.

12.9. The Committee noted previous and ongoing Pharmac engagement with patients, families and advocates for Fabry disease treatment. Specific input on the lived experience of people with Fabry disease and their families was also shared at the Rare Disorders Advisory Committee meeting in March 2023 (section 6.5 to 6.12). This described the substantial impacts of Fabry disease on multiple individuals within families, including the lack of effective treatments in NZ, potential relocation overseas leading to broader family/community separation and disruption to livelihoods, disease burden effects on day-to-day life and future planning, and the grief and trauma of untreated hereditary disease and concerns for future generations.

Māori impact

12.10. The Committee discussed the impact of funding PEG-A for Fabry disease on Māori health areas of focus and Māori health outcomes.

Populations with high health needs

12.11. The Committee discussed the health need(s) of people with Fabry disease among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs.

Background

12.12. The Committee noted that three Fabry disease treatments had been reconsidered by the Committee in recent years, enabling Phamac to continue its process. These treatments are currently listed on Pharmac's Options for Investment (OFI) list:

12.12.1. Agalsidase alfa (AGA-A) was considered by the Rare Disorders Advisory Committee in March 2023. At that time, the Committee had reaffirmed its recommendation to list it with a medium priority based on high health need, a lack of alternative treatments and low-to-moderate evidence, including real-world benefit.

12.12.2. Migalastat was considered by the Rare Disorders Advisory Committee in March 2023, at which time the Committee had reaffirmed its recommendation to list it with a medium priority.

12.12.3. Agalsidase beta (AGA-B) was most recently considered by the Rare Disorders Advisory Committee in May 2024. At that time, the Committee had recommended it be listed with a high priority, noting a high health need as a significant factor in allocating a high priority recommendation. At that time, the Committee considered that AGA-A and AGA-B are similar and could be considered interchangeable in the treatment of Fabry disease.

Health need

12.13. The Committee noted that the biological aspects of Fabry disease have been described extensively in previous clinical advice records. It is a multisystem X-linked lysosomal storage disorder that significantly affects the heart and kidneys, leading to inflammation and eventually, permanent fibrosis. The Committee noted that this progressive disease also causes significant gastrointestinal symptoms, peripheral sensory nerve pain, increases the risk of stroke, and has a significant impact on quality of life of the individual and their family.

12.14. The Committee noted that renal disease is the most difficult aspect of Fabry disease to treat, however, not all individuals with Fabry disease in NZ develop significant renal disease. The Committee noted that some individuals may have other significant Fabry disease features such as cardiac arrhythmias, depending on the genetic variant involved. Members considered that monitoring to distinguish between natural history and disease progression over a number of years is important (eg annual echocardiogram, telemetry, cardiac MRI every three years, assessment of protein loss in urine).

12.15. The Committee considered the patient voice submissions describing the lived experience of individuals and families affected by Fabry disease. Members considered that Fabry disease has a significant impact on younger adults with the disease and the children of affected individuals, noting impacts can include the death of family members, a chronic disease burden, requirement for renal dialysis in some, loss of income, and social consequences.

12.16. Members considered that there are about 27 symptomatic people with Fabry disease in NZ, of which 21 have migalastat-responsive GLA gene variants (some of whom receive treatment within a compassionate access program). Additionally, six to eight people with Fabry disease in NZ do not have responsive variants and would require treatment with enzyme replacement therapy (ERT).

Health benefit

12.17. The Committee noted that pegunigalsidase alfa-iwxj (PEG-A) is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme, a pegylated recombinant form of human α-galactosidase-A. The Committee noted that there is evidence of a longer plasma half-life, greater enzyme activity, greater biodistribution and less liver clearance based on preclinical *in vitro* and *in vivo* studies of PEG-A.

12.18. The Committee noted that PEG-A dosing is 1 mg/kg of body weight administered intravenously once every two weeks, with the application also including data regarding a dose of 2 mg/kg every four weeks. The Committee noted that the four-weekly dosing is currently under review by the European Medicines Authority (EMA) and that two-weekly dosing of PEG-A is approved in some other jurisdictions.

12.19. The Committee noted that PEG-A is manufactured from plant cells and thus thought to be more resistant to potential contamination and biological culture infection, whereas AGA-A and AGA-B are based on human and Chinese hamster cell lines, respectively. The Committee noted international production of AGA-B had been significantly limited by biological culture infection in the past.

12.20. The Committee noted that the submission was predominantly based on two pivotal phase III clinical trials and evidence from three supporting trials, of which two were extensions of the pivotal trials.

12.21. The Committee noted evidence from the BALANCE trial; a phase III, randomised (2:1) double-blind, head-to-head, multi-centre study of PEG-A (n=53) 1mg/kg every two weeks (E2W) compared with AGA-B (n=25) for 24 months in patients with severe Fabry disease (Wallace et al. J Med Genet. 2024;61:520-530). Participants had experienced significant kidney function deterioration while on ERT prior to the study

(AGA-B for ≥ one year and on a stable dose for ≥ six months). The Committee noted that BALANCE aimed to demonstrate non-inferior effectiveness of PEG-A to AGA-B with respect to annualised change in eGFR slope, and thus that the primary outcome was renal disease progression.

12.21.1. The Committee noted that treatment groups were similar, although there were more participants receiving PEG-A vs AGA-B and more women in the PEG-A group. The Committee noted that these women had significant renal disease with a progressive disease course similar to that of males with Fabry disease, and agreed with the post hoc analysis that concluded that the imbalance did not introduce bias.

12.21.2. The Committee noted that these participants had experienced more disease progression and previous treatment than those in other clinical trials of ERT for Fabry disease, and considered that the early development of fibrosis in the disease course can add complexity to assessing outcomes.

12.21.3. The Committee noted that there was no difference between treatment groups in annualised change in eGFR over 24 months (PEG-A -2.51 mL/min/1.73 m^2 and AGA-B -2.16 mL/min/1.73 m^2, difference: -0.36 mL/min/1.73 m^2 [95% CI -2.44, 1.73]), and although eGFR initially worsened for women it then remained stable.

12.21.4. The Committee noted that the authors mentioned cardiac outcomes although these were not reported in detail. The Committee considered that the evidence indicated cardiac outcomes did not worsen in BALANCE trial participants.

12.21.5. The Committee noted that there were fewer infusion reactions in PEG-A group despite all being pretreated for at least one year. The Committee considered that the clinical significance of having a lower incidence of antidrug antibodies (ADAs) was unclear with PEG-A from the data provided.

12.21.6. The Committee considered it reasonable to conclude from BALANCE that PEG-A was at least the same as ERT for the efficacy and safety outcomes assessed.

12.22. The Committee noted evidence from the phase III open-label BRIGHT trial in which 30 (n=24 male) Fabry patients received PEG-A 2mg/kg every four weeks (E4W) for 12 months (Holida et al. J Inherit Metab Dis. 2025;48:e12795). Participants were previously treated with AGA-A or AGA-B (n=23) for at least three years and had remained on a stable dose for at least six months.

12.22.1. The Committee noted that the primary endpoint of BRIGHT was the number of treatment-emergent adverse events (TEAEs). Of 182 reported TEAEs, 33 (in nine patients) were considered treatment-related, all being mild or moderate in severity. The Committee noted that no patients developed de novo ADAs and that plasma PEG-A levels were still detectable out to 28 days.

12.22.2. The Committee noted the primary efficacy analysis (n=29) of renal function, with median eGFR change from baseline over 52 weeks of 1.9 (inter-quartile range 5.9, 1.8) mL/min/1.73 m^2 overall and median eGFR slope of -1.9 (-8.3, 1.9). The Committee considered this change was similar to that reported in BALANCE and noted there is annual decrease in renal function with ageing, regardless of disease.

12.23. The Committee noted the BRIGHT-51 open-label extension of four years duration (in progress) which included 29 Fabry patients who had completed the BRIGHT trial (Bernat et al. Genet. Med. 2023;1(1):100016). The Committee noted that this abstract provided safety data over more than two years and considered this to be consistent with other evidence of safety for PEG-A.

12.24. The Committee noted the other evidence included in the application and identified by Pharmac staff:

- Two phase I/II trials and their corresponding extension study (PB-102-F01, PB-102-F02 and PB-102-F03) from clinical study reports (not published)
- Linhart et al. Orphanet J Rare Dis. 2023;18(1):332
- Hughes et al. Genet. Med. 2023;25(12):100968
- Biegstraaten et al. Orphanet J Rare Dis. 2015:27;10:36
- Azimpour et al. Adv Ther. 2025;42:1421-34

12.25. The Committee considered it reasonable to extrapolate evidence from the BALANCE trial (which was in people with significant renal function deterioration despite receiving ERT treatment) to patients with Fabry disease in NZ more generally, including those who are untreated. The Committee considered this baseline characteristic of BALANCE participants made the evidence more compelling, given that renal deterioration had occurred; in comparison, not all of those at an earlier point in the Fabry disease course would be anticipated to experience renal deterioration over time.

12.26. The Committee considered that the evidence supported non-inferiority of PEG-A to AGA-A and AGA-B for renal outcomes, although noting that this was based on one randomised clinical trial. The Committee considered it unclear from the available evidence whether PEG-A was non-inferior to AGA-A and AGA-B for other outcomes (ie slowed progression of cardiac disease, reduced risk of stroke, longer overall survival, improved HRQoL). However, the Committee considered non-inferiority of other key outcomes was likely given the difficulty treating renal disease in Fabry, and therefore that it was reasonable to extrapolate stability of renal outcomes to other key clinical outcomes in Fabry disease.

12.27. The Committee noted that there is no direct evidence comparing PEG-A vs migalastat, but that PEG-A is thought to be non-inferior based on the ATTRACT trial, which investigated migalastat vs ERT. However, members noted that the evidence is not completely clear. Members therefore considered it reasonable for Pharmac to reconsider and/or seek updated advice on this prior to any funding decision.

12.28. The Committee noted that the evidence base for the E4W dosing regimen of PEG-A was still developing (currently consisting of *in vitro* proof of concept, one published paper, and one abstract reporting on an extension study), however, that the regimen appeared logical based on the half-life of PEG-A. The Committee considered that if deemed to be sufficiently supported by evidence, the E4W dosing interval of PEG-A would be beneficial to patients with Fabry disease (meaning less time off work for the patient) and to clinical services (from reduced use of, and cost of, infusion nurse time and infusion service space), noting that the weight-based dosing will be the same on either ERT regimen. The Committee considered that the EMA appraisal outcome would be useful for Pharmac to consider, once available, although noted that this was predominantly a suitability consideration, as opposed to a fiscal one.

12.29. The Committee considered that if an ERT were funded, it is likely that those receiving ERT would experience improved health-related quality of life regardless of whether they experience Fabry-related complications. However, members considered that the need for frequent medical appointments and infusions could be impactful for some patients.

Suitability

12.30. The Committee noted that PEG-A has a longer shelf life than other ERTs (four years for unopened vials vs two years) and considered the stability data were good for PEG-A.

12.31. The Committee noted that the E2W infusion duration of PEG-A (two hours) is longer than AGA-A (40 minutes) but shorter than AGA-B (three hours).

12.32. The Committee considered that if PEG-A were to be funded, consequences to the health system would include resource impact for initial set-up of patient treatment of eligible patients, review of other patients to consider eligibility (also including renal and cardiac services), associated costs, and ongoing infusion centre resource use.

12.33. The Committee considered that it would be advantageous to have more than one funded treatment for Fabry disease to provide options for patients and aid management of immunogenicity, TEAEs and ADAs (although members noted that the latter could occur less frequently with PEG-A).

12.34. Members considered that if both migalastat and PEG-A were funded, those receiving E4W PEG-A IV might experience better treatment adherence than those receiving oral migalastat every other day, as the latter is more likely to be affected by non-adherence outside of a clinical trial setting.

Cost and savings

12.35. The Committee considered that while there were many health management costs associated with complications from Fabry disease, it was very unlikely these costs would ever offset the cost of treatment to any meaningful degree. The Committee noted that this is a common issue when evaluating the cost-effectiveness for treatments of rare diseases.

Funding criteria

12.36. The Committee considered it appropriate for the funding criteria previously recommended for other ERTs to be applied to PEG-A, as there is no apparent reason for any difference.

Summary for assessment

12.37. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for PEG-A if it were to be funded in New Zealand for Fabry disease. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with Fabry disease who have at least one of the following features: • Renal disease • Cardiac disease • Ischaemic vascular disease • Fabry-related gastrointestinal issues Other manifestation/s with significant HRQoL impacts, as determined by relevant specialist.
Intervention	Pegunigalsidase alfa-iwxj, 1 mg/kg administered once every two weeks. Treatment can continue long-term if the individual is still benefitting.
Comparator(s)	Best supportive care (BSC).

Outcome(s)	• Slower decline in renal function - non-inferior in terms of annual eGFR decline slope to agalsidase beta as per BALANCE trial. Possible[#] other outcomes include: • Slowed progression of cardiac disease • Reduced risk of stroke • Longer survival • Improved HRQoL [#]These outcomes are considered likely (ie improvement vs BSC; non-inferior vs agalsidase beta) based on extrapolation from stability in renal outcomes as per the BALANCE trial.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

13. Onasemnogene abeparvovec for spinal muscular atrophy (SMA), presymptomatic or type 1

13.1. Dr Gina O'Grady, Paediatric Neurologist and expert in treating SMA, attended the discussion as an Observer – Invited Expert. Dr O'Grady left the meeting before the recommendation was made.

Application

13.2. The Committee reviewed an updated application for onasemnogene abeparvovec in the treatment of spinal muscular atrophy (SMA), presymptomatic or type 1. This resubmission was received following previous considerations by the Rare Disorders Advisory Committee. Pharmac staff considered it met Pharmac's Policy principles for rare disorders.

13.3. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

13.4. The Committee **recommended** that onasemnogene abeparvovec for the treatment of SMA, presymptomatic or type 1 be funded with a **high priority** within the context of treatments for rare disorders subject to Special Authority criteria based on the following:

Initial application – (Spinal muscular atrophy) Any relevant practitioner. Approvals for applications meeting the following criteria:
All of the following:

1. Patient has genetic documentation of homozygous SMN1 gene deletion, homozygous SMN1 point mutation, or compound heterozygous mutation; and
2. Either
   - 2.1 Both:
     - 2.1.1. Patient is identified via pre-symptomatic screening; and
     - 2.1.2. Patient has three or less copies of SMN2;
   - 2.2. Or:
     - 2.2.1. Patient is clinically diagnosed with SMA type 1 and is less than (TBD) [months/years] age; and
     - 2.2.2. Patient is not on concurrent risdiplam or nusinersen therapy but may have had prior bridging therapy with risdiplam or nusinersen

13.5. The Committee, in making its recommendation, considered:

13.5.1. onasemnogene abeparvovec is anticipated to be effective lifelong, as it stops the loss of non-replicating motor neuron cells that cause disease progression

13.5.2. onasemnogene abeparvovec would avoid any concerns regarding adherence that may be associated with current treatments and provide suitability benefits compared to currently funded treatments as it is a one-off treatment

13.5.3. access to the treatment would likely be equitable, as newborn screening is used to identify cases and 99% of infants born in New Zealand undergo newborn screening

13.5.4. the high health need of individuals with SMA, and in particular SMA 1 and the difficulty of managing lifelong medicines, acknowledging the patient submission that focused on these issues.

13.6. The Committee noted that proposed Special Authority criteria would be further refined with input from SMA experts outside of this meeting, including defining the age by which treatment should be initiated by for those with SMA type 1.

13.7. The Committee also considered that, were onasemnogene abeparvovec to be funded, the funding criteria for nusinersen and risdiplam would need to be revised to prevent funded use of nusinersen or risdiplam for individuals after the administration of onasemnogene abeparvovec. Any changes to current criteria would be consulted on.

Discussion

Patient lived experience

13.8. The Committee discussed the patient lived experience video submission and expressed gratitude to these individuals and families for sharing their experiences. Specifically, the Committee noted the comments regarding the impact on carers, parents and families of children with SMA including the intensity and frequency of current treatment administration, appointments and management over a lifetime. The Committee heard that a treatment with a single administration such as onasemnogene abeparvovec would make a significant and meaningful difference.

13.9. The Committee also acknowledged that specific input on the lived experience of people with SMA and their families was also shared at the Rare Disorders Advisory Committee meeting in March 2023.

Background

13.10. The Committee noted its previous deferral recommendation (March 2023) pending long-term evidence regarding efficacy and drug safety and concerns regarding the use of combined therapies.

13.11. The Committee considered that since the previous consideration of onasemnogene abeparvovec there have been significant changes in the New Zealand treatment setting, with the inclusion of SMA in newborn screening as of February 2025 and the funding of both nusinersen and risdiplam for the treatment of SMA in April 2023.

Health need

13.12. The Committee noted that in terms of incidence, 60% of people with SMA have type 1, 25% have type 2, and 15% have type 3. They noted the prevalence of type 1 SMA is disproportionately low due to its shortened life expectancy compared to other types of SMA (less than two years) (Russman BS. J Child Neurol. 2007;22:946-51). In New Zealand, the incidence is 2.5 per 100,000 for each of types 1, 2, and 3 (Roxburgh et al. J Neuromuscul Dis. 2025:22143602251319165). The Committee considered the incidence of SMA cases eligible for treatment with onasemnogene abeparvovec would be four to five people per annum.

13.13. The Committee noted that, as of February 2025, the Newborn Metabolic Screening Programme has included screening for SMA. The Committee noted 98.3% of infants in New Zealand are screened in this programme (National Screening Unit, 2023), and were informed that 95% of all infants with SMA are identified in the screening process, but infants who have immigrated and infants with compound heterozygosity would not be diagnosed via this New Zealand based screening. The Committee considered the introduction of newborn screening to be highly relevant, as <1% of infants with SMA are symptomatic at birth, but symptoms generally develop within weeks. As symptom development is associated with a loss of irreversible function and motor neurons, early treatment is vital, and newborn screening allows for this due to earlier diagnosis.

13.14. The Committee considered that, with early diagnosis of SMA via the Newborn Metabolic Screening Programme and the funding of disease modifying treatments, that more people born with SMA type 1 would be anticipated to have significantly increased life expectancy.

13.15. The Committee noted the Roxburgh et al. 2025 study that reported high health resource utilisation among children with SMA. The need for ambulation/mobility, ventilation, tube feeding, and scoliosis management is high and surgery for scoliosis is common. Children have frequent hospital inpatient admissions, outpatient visits, and operating theatre visits.

Health benefit

13.16. The Committee considered that its discussion should focus primarily on the evidence reporting on the efficacy of onasemnogene abeparvovec in newborn treatment, given that SMA is now included in New Zealand's Newborn Screening Programme.

13.17. Regarding the efficacy of onasemnogene abeparvovec, the Committee noted the following evidence:

13.17.1. Strauss et al. Nat Med. 2022;28:1381-89 (SPR1NT 1; considered previously in 2023): A phase III, multicentre, single-arm study investigating the safety and efficacy of onasemnogene abeparvovec for presymptomatic children with two SMN2 copies treated at ≤6 weeks of life (n = 14). Efficacy was compared with a matched natural-history cohort (n = 23). All enrolled children were alive and non-reliant on feeding or respiratory support at the 18-month follow up. The Committee noted, prior to 18-months of age, that all participants achieved independent sitting for at least thirty seconds, 11 participants stood independently, and nine participants walked independently.

13.17.2. Strauss et al. Nat Med. 2022;28:1390-97 (SPR1NT 3; considered previously in 2023): A phase III, multicentre, single-arm study investigating the safety and efficacy of onasemnogene abeparvovec for presymptomatic children with three SMN2 copies treated at ≤6 weeks of life (n = 15). Efficacy was compared with a matched natural-history cohort (n = 81). All enrolled children were alive and non-reliant on feeding or respiratory support at the 24-month follow up. The Committee noted, prior to 24-months of age, that 14 participants achieved independent sitting for at least thirty seconds, 15 participants stood independently, and 14 participants walked independently.

13.17.3. Servais et al. J Neuromuscul Dis. 2024;11:425-42: A prospective, multinational study of people with SMA types 1-3, pre- and post-symptomatic with SMN2 copies ranging from one-four who received only onasemnogene abeparvovec monotherapy using data from the RESTORE registry (n = 168). 80 participants had two SMN2 copies, 70 had three SMN2 copies, and 98 participants were identified by newborn screening. Participants were treated between one and ten months of age, with a median follow-up of 12.24 months.

For participants with two SMN2 copies who were also diagnosed via newborn screening, all (n = 42) survived without requiring respiratory or feeding support, the median age for independent sitting for at least 30 seconds was 10.63 months, and the median age for independent walking was 15.4 months. At 12 months follow-up, 162/168 of participants were fed exclusively orally.

13.17.4. Servais et al. MDA conference, 2024;161P: Conference proceedings of the long-term safety of onasemnogene abeparvovec in people with SMA, using the RESTORE registry (n =140). All drug-related adverse events (AEs) were identified within three months of drug administration and were not clinically significant (ie. blood test abnormalities without clinical symptoms that were managed). Thrombotic microangiopathy (TMA) was reported for three participants (2%) within three months of administration. The Committee noted that all TMA cases recovered, and one individual experienced persistent hypertension. The Committee considered that there were a reasonable number of AEs reported, but that this is not unusual in clinical trials.

13.18. The Committee considered that, in comparison to the natural history placebo group in the SPR1NT trials (in which 26% of participants survived to 18-months of age), the survival and motor milestone achievements in the group receiving onasemnogene abeparvovec was clinically significant.

13.19. The Committee considered that there is now longer-term evidence on the efficacy and safety of onasemnogene abeparvovec (ie. five years for individuals identified through newborn screening, and up to eight years for those identified following symptom onset) than there was for nusinersen and risdiplam when they were funded in New Zealand.

13.20. The Committee considered that onasemnogene abeparvovec is non-inferior to nusinersen and noted that fewer individuals required feeding support on onasemnogene abeparvovec than nusinersen when indirectly comparing the results from non-head-to-head trials. The Committee considered that treatments prevent motor neuron loss, which is a predictor of long-term outcomes. The Committee also considered that onasemnogene abeparvovec may be superior in maintaining bulbar function compared to other available treatments but noted a lack of strong evidence to support this consideration. The Committee considered that the noted evidence to be of high quality and highly relevant to the New Zealand context.

13.21. The Committee noted international recommendations from health technology assessment agencies regarding age restrictions for access to treatment with onasemnogene abeparvovec:

13.21.1. Australia (PBAC): recommended treatment for SMA in patients aged up to 9 months, with Type I SMA or pre-symptomatic patients with 1-3 copies of the SMN2 gene.

13.21.2. Scotland (SMC): no age restriction for individuals with type 1 SMA or who are presymptomatic and have zero to three SMN2 copies.

13.21.3. Canada (CADTH): recommended for those aged less than three months for infants with one to three copies of SMN2 who do not require permanent feeding or ventilation support.

13.21.4. England/Wales (NICE): recommended for those aged less than six months for presymptomatic infants with zero to three SMN2 copies, and aged seven to twelve months if treatment is agreed by the national multidisciplinary team and the supplier provides treatment according to the UK commercial arrangement.

13.22. The Committee considered that there is no evidence to support combination therapies in the treatment of SMA, but that bridging therapy with nusinersen or

risdiplam may be appropriate immediately following diagnosis but prior to any treatment with onasemnogene abeparvovec to prevent loss of function until AAV9 antibody test results are received and the administration of onasemnogene abeparvovec can be organised.

13.23. The Committee was informed that, in terms of uptake estimates, in Australia, 85% of families of children with SMA opt for treatment with onasemnogene abeparvovec, and less than 5% of children have the AAV9 antibody that precludes treatment with onasemnogene abeparvovec.

13.24. The Committee was informed that there is currently an estimated 1:1 split in the treatment of SMA with nusinersen or risdiplam in New Zealand, however, noted that Pharmac staff would confirm the split in treatment based on most recent dispensing data.

13.25. The Committee considered that there may be a quality-of-life benefit gained from treatment with onasemnogene abeparvovec compared to currently funded treatments as it is a single administration given intravenously, meaning adherence is automatic at just one point in time. In contrast, nusinersen requires a life-long dosing schedule of three intrathecal administrations per year, whilst risdiplam requires daily oral administration. Required ongoing administration of these two medicines increases the possibility of incomplete adherence over time.

13.26. The Committee considered that as a result of extended life expectancy in individuals with SMA who receive funded treatment, progressive effects such as spinal kyphosis and scoliosis may be seen more often. The Committee considered that this would also be impacted by poor adherence to currently funded treatments. The Committee considered that these effects would be experienced less by people with onasemnogene abeparvovec than by people treated with nusinersen and risdiplam treated at the same age. Members reprised how progressive spinal deformities could impede ongoing intrathecal administration of nusinersen, which is not an issue for onasemnogene abeparvovec or risdiplam.

Suitability

13.27. The Committee considered that day-stay admission would be suitable for treatment with onasemnogene abeparvovec.

13.28. The Committee considered onasemnogene abeparvovec (one single intravenous infusion) to provide superior suitability benefits than nusinersen (ongoing intrathecal administration three times per annum, more difficult with progressive spinal deformities) and risdiplam (continuous daily oral administration) as it is a single administration avoiding daily oral administration difficulties in young children (risdiplam) or avoiding ongoing hospitalisations for intrathecal administration under general anaesthesia (with inherent risks).

Cost and savings

13.29. The Committee considered that corticosteroid therapy and monitoring post-administration would be required for treatment of SMA with onasemnogene abeparvovec, as most adverse events occur within the first three months of administration.

13.30. The Committee considered that preventative effects of one-off onasemnogene abeparvovec for SMA would likely be lifelong, as motor neurons are a stable cell population and do not replicate. The treatment prevents the loss of motor neurons, and the most significant predictor of outcomes is the age when treated, with SMN2 copy number the second most significant predictor. The Committee also considered that available outcome data to date extends to eight years, with individuals maintaining previously achieved milestones and continuing to gain new ones.

13.31. The Committee considered that there would likely be marked cost-savings to the health system associated with onasemnogene abeparvovec treatment, particularly regarding the currently required ongoing maintenance appointments for individuals using nusinersen or risdiplam therapy. The Committee considered that the cost-savings associated with onasemnogene abeparvovec would likely be similar to those of nusinersen and risdiplam, exclusive of the administration appointments needed for nusinersen. Other savings would be gained from a reduction in adherence-related issues, the non-requisite of sedation or general anaesthesia (unlike nusinersen), and singular day-stay admission for treatment receipt.

Funding criteria

13.32. The Committee considered that the special authority criteria initially provided by the supplier be revised with respect to age restrictions, specification of clinical presentation of disease, and allowing bridging therapy whilst excluding concurrent therapy. The Committee considered that these changes would need to be made to reflect the need of the population with pre-symptomatic and type 1 SMA, ensuring that the criteria do not create an inadvertent barrier to access. The Committee also considered that the details of the special authority criteria would require further input from SMA experts.

Summary for assessment

13.33. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for onasemnogene abeparvovec if it were to be funded in New Zealand for pre-symptomatic or early type 1 SMA. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	• People with SMA type I who have been diagnosed symptomatically • People with pre-symptomatically diagnosed SMA who have ≤3 *SMN2* gene copies. 4-5 cases per year based on current birth rates
Intervention	Onasemnogene abeparvovec, at the recommended dose is 1.1 × 10E14 vector genomes (vg)/kg as a one-time (or 'one off') treatment. The onasemnogene abeparvovec kit consists of 2 vial sizes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0 × 10E13 vg/mL. The appropriate onasemnogene abeparvovec dose and kit is determined by an individual's body weight.
Comparator(s) (NZ context)	Nusinersen – six doses in the first year of treatment, three doses in subsequent years of treatment. Each dose is one single-use vial of 12 mg nusinersen-equivalent, administered via intra-thecal injection. Risdiplam – once daily oral dose as determined by age and body weight
Outcome(s)	Compared to currently funded treatments, there is no evidence to support onasemnogene abeparvovec providing a superior health benefit. The main comparative benefit is suitability, in which onasemnogene abeparvovec provides complete adherence that is unlikely to be experienced with alternative treatments – possibly affecting treatment efficacy long-term.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)	

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.