

5.10 RAVULIZUMAB, Solution concentrate for I.V. infusion 300 mg in 30 mL, Ultomiris[®], Alexion Pharmaceuticals Australasia Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested Section 100 listing for ravulizumab for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus eculizumab and a cost-utility analysis versus best supportive care (BSC).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with paroxysmal nocturnal haemoglobinuria (PNH). The submission stated that the proposed clinical criteria to determine treatment eligibility for ravulizumab are the same as the existing criteria for adult patients with PNH treated with eculizumab via the Life Saving Drugs Program (LSDP)
Intervention	Ravulizumab, administered by infusion every 8 weeks
Comparator	Primary Comparator: eculizumab, administered by infusion every 2 weeks Secondary Comparator: best supportive care (BSC)
Outcomes	Ravulizumab vs eculizumab: - Transfusion avoidance, haemolysis (measured by LDH change); breakthrough haemolysis; quality of life, stabilised haemoglobin Ravulizumab vs BSC: - Transfusion avoidance, quality of life, haemolysis (LDH change)
Clinical claim	In adults with PNH, ravulizumab is non-inferior to eculizumab in terms of efficacy and safety; and significantly reduces breakthrough haemolysis (based on meta-analysis) compared to eculizumab. In adults with PNH, ravulizumab is superior to BSC in terms of efficacy and inferior to BSC in terms of safety.

Source: Table 1, pp3-4 of the submission.

BSC, best supportive care; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria

2 Background

Registration status

- 2.1 Ravulizumab 10 mg/mL (300 mg in 30 mL) was approved by the TGA for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria on 8 October 2019.
- 2.2 The submission noted that an application for a higher strength dose of ravulizumab (100 mg/mL) was submitted to the TGA in February 2020, with approval anticipated in the third quarter of 2020. The higher strength doses consist of 300 mg in 3 mL and 1100 mg in 11 mL vials, which allow for use of fewer vials and a shorter infusion time (30-55 min vs 120-140 min) for maintenance doses.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Population and disease

- 3.1 Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired, life-threatening disease of the blood associated with a clonal disorder of the haemopoietic stem cell. The condition is characterised by chronic haemolysis, which is responsible for most of the clinical manifestations of the disease, including severe anaemia, life threatening thromboses, kidney damage and failure and disabling fatigue. The median age of patients at diagnosis is 35-40 years. In 2010, the PBAC accepted that patients with classic PNH had a significant reduction in age-specific life expectancy (Section 11, eculizumab, Public Summary Document, July 2010 PBAC meeting). Previously published trends suggest improved life expectancy over time for patients with PNH, given improvements in modern supportive treatments (de Latour 2008). Given the lack of contemporary supportive care data, the magnitude of the reduction in life-expectancy for current PNH patients remained unclear.
- 3.2 Ravulizumab, a new long-acting anti-C5 monoclonal antibody that antagonises terminal complement at the same C5 epitope as eculizumab, is administered as a weight based dose. The regimen starts with a loading dose, followed two weeks later with a maintenance dose, and then ongoing maintenance dosing every 8 weeks, and therefore has a lower treatment burden than eculizumab, which requires ongoing maintenance dosing every two weeks.
- 3.3 The submission positions ravulizumab as an alternative to eculizumab or BSC for the treatment of PNH, targeting the PNH population that would meet the current LSDP eligibility conditions for the use of eculizumab: PNH granulocyte clone size of 10% or larger, lactate dehydrogenase (LDH) levels at least 1.5 times the upper limit of normal, and at least one symptom of clinical complications associated with PNH. Patients with severe aplastic anaemia or other conditions that may compromise a response to therapy are excluded from treatment under the proposed restriction.

Previous PBAC consideration

- 3.4 This is the first submission to the PBAC for ravulizumab. Eculizumab, one of the proposed comparators for ravulizumab, was considered by the PBAC for use in PNH in July 2008, March 2009 and July 2010. Eculizumab was recommended for inclusion on the Life Saving Drugs Program (LSDP) in August 2010. The sponsor of ravulizumab is also the sponsor of eculizumab.

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Table 2: Summary of previous PBAC submissions for eculizumab in PNH

PBAC Meeting Date	Basis of outcome
July 2008	Rejected for PBS listing on the basis of an unacceptably high and highly uncertain estimated cost per additional death avoided over a 2-year period. Also rejected for consideration for the LSDP on the basis that it did not fulfil specific eligibility criteria for LSDP listing.
March 2009 and July 2010	Rejected for PBS listing on the basis of an unacceptably high and highly uncertain cost-effectiveness. The PBAC considered that eculizumab met the criteria for inclusion on the LSDP but that specific requirements for initiation and continuation of treatment would need to be developed by independent experts to identify those patients with PNH who would benefit most from treatment with eculizumab.
August 2010 (special meeting)	PBAC considered that eculizumab met all the LSDP criteria following identification of PNH patients who would benefit most from treatment with eculizumab. The PBAC considered that eculizumab fulfilled all criteria of the LSDP, including the criterion that the lifespan of a patient will be substantially extended as a direct consequence of the use of the drug.
[REDACTED]	[REDACTED]

Source: Table 5, p22 of the submission.

Abbreviations: LSDP, life saving drugs program; PNH, paroxysmal nocturnal haemoglobinuria

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Requested listing

4.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
RAVULIZUMAB 300mg/30 mL IV infusion	1	1	0	Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	Ultomiris® Alexion Pharmaceuticals

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Category / Program:	Section 100 – Highly Specialised Drugs Program (Community Access Public/Private)
PBS Indication:	Paroxysmal nocturnal haemoglobinuria (PNH)
Treatment phase:	Initial treatment- <i>Initial 1 (new patient)</i>
Restriction:	Authority required – written
Treatment criteria:	Patient must be treated by a haematologist or in consultation with a haematologist ; or <i>Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details</i>
Clinical criteria:	<p>Patient must have a diagnosis of PNH established by flow cytometry and patient must have a PNH granulocyte clone size equal to or greater than 10%, AND</p> <p>Patient must have a raised LDH/lactate dehydrogenase value at least 1.5 times the upper limit of normal ULN, AND</p> <p>Patient must have received/ will receive a meningococcal vaccination at the time of initiating treatment that is documented in the patient's medical records AND</p> <p>Patient must have experienced a thrombotic or/ embolic event which required the institution of therapeutic anticoagulant therapy, OR</p> <p>Patient must have been transfused with at least 4 units of red blood cells in the last 12 months, OR</p> <p>Patient must have chronic or /recurrent anaemia, where causes other than haemolysis have been excluded, and demonstrated by more than one together with multiple red blood cell measurements of less than or equal to not exceeding 70 g/L in the absence of anaemia symptoms, OR</p> <p>Patient must have debilitating shortness of breath and/or chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded, OR</p> <p>Patient must have a history of renal insufficiency, demonstrated by an eGFR less than or equal to 60mL/min/1.73m², where causes other than PNH have been excluded, OR</p> <p>Patient must have recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded, AND</p> <p>Patient must not have a small granulocyte clone size: (a granulocyte clone size below 10%), AND</p> <p>Patient must not have aplastic anaemia (<i>having at least 2 of the following indicates the presence of aplastic anaemia: neutrophil count below 0.5 x 10⁹/L, platelet count below 20 x 10⁹/L, reticulocytes below 25 x 10⁹/L, or severe bone marrow hypocellularity</i>), AND</p> <p>Patient must not have another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by therapy (for example e.g. acute myeloid leukaemia or /high-risk myelodysplastic syndrome), AND</p> <p>Patient must not have another medical condition that might reasonably be expected to compromise a response to therapy, AND</p> <p>Patient must not be currently participating in a clinical trial</p>
Population criteria:	Patients must be aged 18 years or older
Administrative Advice Prescribing instructions:	<p><u>Note:</u></p> <p>At the time of authority application, medical practitioners request the appropriate number of vials to provide sufficient drug for 2 infusions (1 loading dose plus 1 maintenance doses) according to the specified dosage in the approved Product Information (PI).</p> <p><i>At the time of the authority application, medical practitioners should request the appropriate number of vials, to provide for a single infusion of 300 mg per dose sufficient drug to cover the loading dose and 1 dose after the loading dose based on the patient's weight and the Product Information. For a patient weight range of 60-100-kg, request ■ Vials and Nil repeats. For patients weighing less than ≥40 to <60 kg, no more than ■ vials should be prescribed. For patients weighing more than 100 kg, an increased maximum quantity should be sought. A maximum quantity of ■ vials may be approved.</i></p> <p>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved Product Information will not be approved.</p>

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Administrative Advice	<p>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised.</p>
Caution:	<p>WARNING: Eculizumab Ravulizumab (sponsor) - This drug increases the risk of meningococcal infections (sepsis and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.</p>

Requested restriction for ravulizumab – initial treatment for complement inhibitor-naïve patients

Source: Table 13, p37 of the submission.

Requested restriction for ravulizumab – initial treatment for patients transitioning from eculizumab to ravulizumab (abridged)

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
RAVULIZUMAB, 300mg/30mL IV infusion	1	1	5	Public hospital: \$ Private hospital: \$	Ultomiris® Alexion Pharmaceuticals
Category / Program:	Section 100 – Highly Specialised Drugs Program (Community Access Public/Private hospital)				
Condition:	Paroxysmal nocturnal haemoglobinuria				
PBS Indication:	Paroxysmal nocturnal haemoglobinuria				
Treatment phase:	Initial treatment- Initial 2 (switching from eculizumab)				
Restriction:	Authority required – written				
Treatment criteria:	Patient must be treated by a haematologist or in consultation with a haematologist ; or Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details				
Clinical criteria:	Patient must have been receiving supply of eculizumab under the LSDP Australian Government's Life Saving Drugs Program eligibility criteria for this condition.				
Population criteria:	Patients must be aged 18 years or older				

Requested restriction for ravulizumab – continuing treatment including grandfathering provision (abridged)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Ravulizumab, 300mg/30ml IV infusion	1	5	Public hospital: \$ Private hospital: \$	Ultomiris® Alexion Pharmaceuticals
Category/Program:	Section 100 – Highly Specialised Drugs Program (Community Access)			
PBS indication:	Paroxysmal nocturnal haemoglobinuria			

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Treatment phase:	Continuing treatment
Restriction:	Authority required – written
Treatment criteria:	Patient must be treated by a haematologist or in consultation with a haematologist ; or <i>Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details</i>
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition previously qualified for supply of ravulizumab for this condition under the initial treatment restriction, OR</p> <p>Patient must have received non-LSDP subsidised treatment with this drug for this condition as part of the clinical trial programme prior to [XX listing date] (separate grandfather treatment listing to be proposed by Secretariat for such patients; details still to be determined) AND</p> <p>Patient must not be currently participating in a clinical trial</p> <p>Patient must demonstrate clinical improvement or stabilisation of the condition based on clinical data on the following monitoring requirements provided every 12 months (<i>further refinement by the Secretariat would be required with respect to how many need to be met, what values/outcomes must be met, what evidence is acceptable, etc.</i>):</p> <p>haemoglobin (Hb); platelets; white cell count; reticulocytes; neutrophils; granulocyte clone size; lactate dehydrogenase (LDH); urea and electrolytes; eGFR; iron studies; thrombosis; transfusions; anaemia; pulmonary insufficiency; renal insufficiency; smooth muscle spasm; transfusion history; quality of life (narrative including fatigue); PNH related medications; anecdotal information from treating physician; other conditions/diagnosis; vaccination date.</p>
Population criteria:	Patients must be aged 18 years or older

Source: Table 15, pp39-40 of the submission.

- 4.2 The submission noted that less than 10,000 Australian patients are currently treated with ravulizumab through participation in the extension phase of three ravulizumab clinical trials. The sponsor requested a grandfathering provision for these less than 10,000 patients. There was no assessment of these patients against eligibility criteria in the requested PBS restriction.
- 4.3 The requested restrictions are narrower than the approved TGA indication (adults with PNH), with a number of additional specific clinical criteria included in the requested restrictions.
- 4.4 Unlike eculizumab, which is indicated for use in both children and adults, the TGA approved indication and the requested restriction for ravulizumab limits treatment to adults (aged 18 years and older), as the safety and efficacy of ravulizumab in children with PNH has not been established. The ESC also noted that ravulizumab is not recommended for use in pregnancy.
- 4.5 The proposed eligibility criteria were similar to those used in the included ravulizumab trials, with LDH required to be greater than 1.5 times the upper limit of normal prior to treatment with a complement inhibitor. However, the trial criteria specified diagnosis of PNH confirmed by granulocyte or monocyte clone size of $\geq 5\%$, compared to $\geq 10\%$ for the requested restriction.
- 4.6 The proposed clinical criteria for treatment with ravulizumab are the same as the existing criteria for adult patients with PNH, treated with eculizumab via the LSDP.
- 4.7 The sponsor stated that they anticipate that ravulizumab will be considered for inclusion on the LSDP, should ravulizumab be deemed to be clinically effective but not

cost-effective by the PBAC. The PBAC cannot advise if a drug is appropriate for listing on the LSDP.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated eculizumab as the main comparator, and BSC as an additional comparator. Eculizumab is an anti-C5 monoclonal antibody, administered as an IV infusion every 14 days, with more frequent dosing (every 12 days) for patients who experience breakthrough haemolysis. Although not listed on the PBS for PNH, eculizumab underwent clinical evaluation by the PBAC for efficacy and safety and economic evaluation for cost-effectiveness against best supportive care prior to its recommendation for inclusion on the Life Saving Drugs Program (LSDP) in 2010 for PNH.
- 5.2 The ESC considered eculizumab was the appropriate main comparator (as opposed to BSC), given the similarities in patient eligibility criteria between the two treatments and that it was estimated around █% of current eculizumab use on the LSDP would be replaced by ravulizumab, should ravulizumab be recommended for PBS listing.
- 5.3 BSC was nominated as a secondary comparator to determine the cost-effectiveness of a PBS listing for ravulizumab, as there is currently no PBS-listed medicine specifically for the treatment of patients with PNH. BSC reduces the systemic effects of anaemia, intravascular haemolysis, and thromboembolic disease, but does not treat the underlying condition. BSC treatments include transfusion of red blood cells, iron and/or folic acid therapy, steroids (androgens, glucocorticoids, anabolic steroids) and anticoagulants (coumarins and heparins).
- 5.4 The ESC considered BSC was an appropriate secondary comparator, given eculizumab is not PBS-listed for PNH. The ESC noted that all the data comparing ravulizumab to BSC is indirect, however it considered it would be unethical to conduct a clinical trial of ravulizumab vs BSC, given eculizumab is the current standard of care in PNH.
- 5.5 The ESC advised that given eculizumab is clinically the most appropriate comparator, consideration should be given as to whether eculizumab for PNH could be moved from the LSDP to the PBS, noting it is currently available on the PBS for a different indication (atypical haemolytic uremic syndrome (aHUS)). The ESC considered if eculizumab for PNH was also listed on the PBS, it would remove a large amount of uncertainty resulting from the comparison with BSC, given the multiple naïve indirect comparisons involved and no direct PBS reference point for price.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor Hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented the natural history of the disease, how the drug compares to eculizumab in relation to clinical outcomes, patients' preference for the eight-weekly dosing regimen and other matters.
- 6.2 The PBAC considered the hearing was informative as it provided a clinical perspective on treating this uncommon disease. The PBAC also noted additional comments provided by the clinician regarding a preference for funding ravulizumab through the LSDP as opposed to the PBS, primarily based on the LSDP's capacity for data analysis of clinical value to inform the future use of these medicines. However, the PBAC noted data collection and analysis is also possible for medicines subsidised on the PBS. collected.

Consumer Comments

- 6.3 The PBAC noted and welcomed the input from individuals (36), health professional (7) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the main benefit of treatment with ravulizumab was the reduced dosing regimen of eight-weekly infusions, compared to fortnightly infusions with eculizumab.
- 6.4 The PBAC noted the advice received from the PNH Support Association of Australia (PNHSAA) clarifying the likely use of ravulizumab in clinical practice. The PBAC specifically noted the advice that the use of ravulizumab may increase the convenience of receiving treatment for patients, caregivers and the hospital system as a result of the eight-weekly infusion regimen.

Clinical trials

- 6.5 The submission was based on two head-to-head randomised non-inferiority trials comparing ravulizumab to eculizumab, Trial 301 (treatment-naïve patients) and Trial 302 (previously stable on treatment with eculizumab). A supportive post-hoc subgroup analysis of patients meeting eligibility criteria for eculizumab via the LSDP was conducted for patients in Trial 301.
- 6.6 Two indirect comparisons of ravulizumab and BSC/placebo were presented, one based on the meta-analysed results of the two ravulizumab trials (Trials 301 and 302) and one placebo-controlled eculizumab trial (TRIUMPH), with eculizumab as a common reference; and a second using the results from Trial 301 only compared to TRIUMPH, with eculizumab as common reference (treatment-naïve population).
- 6.7 Details of the trials presented in the submission are provided in the table below.

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Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ravulizumab vs eculizumab		
Trial 301	CSR ALXN1210-PNH-301 A Phase 3, Randomized, Open-Label, Active-Controlled Study Of ALXN1210 Versus Eculizumab In Complement Inhibitor-Naive Adult Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH)	May 2018
	CSR ALXN1210-PNH-301 A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naive adult patients with paroxysmal nocturnal haemoglobinuria (PNH)	May 2019
	Addendum to clinical study report (52-week data update)	
	Lee JW, de Fontbrune FS et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Lee JW, Bachman ES, et al. Immediate, complete and sustained inhibition of C5 with ALXN1210 reduces complement-mediated hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH): Interim analysis of a dose-escalation study.	<i>Blood</i> 2019; 133(6): 530-539 <i>Blood</i> 2016; 128:2428
Trial 302	CSR ALXN1210-PNH-302 A Phase 3, Randomized, Open-Label, Active-Controlled Study Of ALXN1210 Versus Eculizumab In Adult Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH) Currently Treated With Eculizumab.	May 2018
	CSR ALXN1210-PNH-302 A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal haemoglobinuria (PNH) currently treated with eculizumab. Addendum to clinical study report (52-week data update)	May 2019
	Kulasekararaj, A., et al. One-Year Efficacy and Safety from a Phase 3 Trial of Ravulizumab in Adult Patients with Paroxysmal Nocturnal Haemoglobinuria Receiving Prior Eculizumab Treatment.	<i>Blood</i> 2019; 134 (Supplement 1): 2231
	Kulasekararaj AG, Hill A, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: The 302 study.	<i>Blood</i> 2019; 133(6): 540-549.
Eculizumab vs BSC/placebo		
TRIUMPH	CSR C04-001. TRIUMPH: A Haemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Haemoglobinuria Patients Hillmen P, et al. The complement inhibitor eculizumab in paroxysmal nocturnal haemoglobinuria. Hill A, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria.	July 2006 <i>New England J Med</i> 2006; 355(12): 1233-1243. <i>British Journal of Haematology</i> 2010; 149(3): 414-425.

Source: Table 21, pp53-55 of the submission.

6.8 The key features of the randomised trials are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation ^a
Ravulizumab vs eculizumab						
Trial 301 ^b	246	Multicentre, randomised, open label, active controlled noninferiority trial 26 weeks	Unclear	Treatment naïve	Transfusion avoidance, LDH normalisation, BTH, stabilised haemoglobin, change in FACIT-fatigue score, % change in LDH. EORTC QLQ-C30	Weight distribution of patients
Trial 302	195	Multicentre, randomised, open label, active controlled noninferiority trial 26 weeks	Unclear	Stable with eculizumab treatment	Transfusion avoidance, % change in LDH, BTH, stabilised haemoglobin, change in FACIT-fatigue score, EORTC QLQ-C30	EORTC QLQ-C30 scores
Meta-analysis	441	Included Trial 301 and trial 302				RD for BTH (ravu), BTH events (ecu)
Indirect comparison: Eculizumab vs placebo/best supportive care, eculizumab common reference						
TRIUMPH	87	Multicentre, randomised, double blind, placebo controlled trial 26 weeks	High	Treatment naïve	Haemoglobin stabilization, blood transfusions, transfusion avoidance ^c , LDH AUC, change in FACIT-fatigue score ^c , % change in LDH ^c , EORTC QLQ-C30	EORTC QLQ-C30 scores

Source: Section 2.4.1, pp64-78 of the submission.

Abbreviations: AUC, area under the curve; BTH, breakthrough haemolysis; ecu, eculizumab; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; ravu, ravulizumab; RD, risk difference.

^a BTH results and EORTC QLQ-C30 scores from Trial 302 were used in the modelled evaluation of ravulizumab and eculizumab; all other modelled outcomes were also used in the modelled evaluation of ravulizumab and best supportive care

^b A post-hoc subgroup analysis of 208 patients from Trial 301 who would meet the proposed PBS eligibility criteria for ravulizumab was also presented.

^c Outcomes included in indirect comparison (transfusion avoidance, change from baseline in FACIT-fatigue score, % change from baseline in LDH).

6.9 Although both ravulizumab trials had an open-label design, the primary outcome measures were biochemical and objective, and were unlikely to be affected by unblinding. However, awareness of treatment allocation may have affected the reporting of subjective patient outcomes (e.g. safety, quality of life).

6.10 The TRIUMPH trial was the primary evidence presented in the PBAC submission for eculizumab evaluated by the PBAC in July 2008 and March 2009. In the TRIUMPH trial, 22% of the placebo group withdrew from treatment due to a perceived lack of efficacy but remained in the study for monitoring, compared to 5% of the eculizumab group, which suggests potential unblinding of treatment groups. Knowledge of treatment allocation may have led to differences in disease management between arms; and also the reporting of adverse events and quality of life outcomes. There is potential for survivor bias due to differential discontinuation.

- 6.11 There are currently no long-term studies of disease progression and survival in patients treated with ravulizumab, beyond the one-year data available from the extension periods of the ravulizumab clinical trials.
- 6.12 The submission’s claim of non-inferior survival of ravulizumab compared to eculizumab, and superior survival compared to best supportive care was entirely based on the available survival data for eculizumab, and an assumption that non-inferiority for measured surrogate outcomes may be extended to survival. The survival data presented in the submission is summarised in Table 14 below. In the economic model, the submission used survival data from a retrospective study of eculizumab versus a matched historical control (Kelly 2011) as a proxy for ravulizumab. The ESC noted the survey of eculizumab survival data presented in the submission is incomplete (see also paragraph 6.30).
- 6.13 The ESC noted the draft report of the LSDP Review of eculizumab stated that [REDACTED], whilst also noting that the studies had a significant risk of bias.

Comparative effectiveness

- 6.14 Results from the comparison of ravulizumab and eculizumab for the outcomes of LDH normalisation, % LDH change from baseline, proportion of patients experiencing transfusion avoidance, BTH and haemoglobin stabilisation, and change from baseline in quality of life (FACIT-fatigue scale) are presented in the tables below. All efficacy outcomes were within the bounds of the pre-specified non-inferiority margins from the trials, and results indicated non-inferiority of ravulizumab to eculizumab for all measured outcomes.

Table 5: LDH normalisation in the ravulizumab trials

Trial ID	LDH Normalisation (adjusted prevalence, 95% CI)		Odds Ratio (95% CI)
	Ravulizumab	Eculizumab	
Trial 301	0.536 (0.459, 0.612)	0.494 (0.417, 0.570)	1.187 (0.796, 1.769)
Trial 302	0.608 (0.508, 0.700)	0.568 (0.467, 0.664)	1.179 (0.737, 1.887)

Source: Table 55, pp115-118 of the submission; Trial 302 clinical study report.

Abbreviations: CI, confidence interval; NA, not applicable; SE, standard error; ULN, upper limit of normal.

Note: The upper limit of normal for LDH is 246 U/L. LDH normalisation was measured as 1 x ULN, from Day 29 through Day 183. Estimation was based on a GEE approach. The model included the following terms: treatment group, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable).

Table 6: LDH % change from baseline at Week 26

Trial ID	Ravulizumab LDH			Eculizumab LDH			Treatment difference, % (95% CI)
	Baseline, mean U/L (SD)	Endpoint	% Change (SE)	Baseline	Endpoint	% Change (SE)	
Trial 301	1633.53 (778.75)	NR	-76.84% (1.58%)	1578.30 (727.06)	NR	-76.02% (1.61%)	-0.83% (-5.21, 3.56)
Trial 302	228.01 (48.71)	NR	-0.82% (3.03%)	235.22 (49.71)	NR	8.39% (3.04%)	-9.21% (-18.84, 0.42)

Source: Table 55, pp115-118 of the submission, Trial 301 and 302 clinical study reports.
Abbreviations: CI, confidence interval; NR, not reported; SE, standard error.

Table 7: Proportion of patients experiencing transfusion avoidance, breakthrough haemolysis, stabilised haemoglobin to Week 26 of the ravulizumab trials

Trial ID	Ravulizumab n/N (%)	Eculizumab n/N (%)	Treatment difference (95% CI)
Transfusion avoidance			
Trial 301	92/125 (73.6%)	80/121 (66.1%)	6.8% (-4.66, 18.14)
Trial 302	85/97 (87.6%)	81/98 (82.7%)	5.5% (-4.27, 15.68)
Breakthrough haemolysis^a			
Trial 301	5/125 (4.0%)	13/121 (10.7%)	-6.7% (-14.21, 0.18)
Trial 302	0/97 (0%)	5/98 (5.1%)	-5.1% (-18.99, 8.89)
Stabilised haemoglobin (avoidance of a ≥ 2 g/dL decrease in haemoglobin level)			
Trial 301	85/125 (68.0%)	78/121 (64.5%)	2.9% (-8.80, 14.64)
Trial 302	74/97 (76.3%)	74/98 (75.5%)	1.4% (-10.41, 13.31)

Source: Table 55, pp115-118 of the submission.

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; n, number of participants with event; N, total participants in group; ULN, upper limit of normal

^a Breakthrough haemolysis was defined in the trials as ≥ 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, major adverse vascular event; in the presence of elevated LDH $\geq 2 \times$ ULN, after prior LDH reduction to $<1.5 \times$ ULN on therapy, through Week 26

Note: For transfusion avoidance and stabilised haemoglobin outcomes, percentage and CI for the difference of percentages are calculated using stratified Newcombe confidence interval method. The stratification factors were observed stratification groups of pRBC/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH levels in Trial 301, and transfusion history (yes/no) within 1 year prior to first dose of study drug in Trial 302.

Table 8: Change from baseline in FACIT-fatigue total score in the ravulizumab trials

Trial ID	Ravulizumab Total score			Eculizumab Total score			Treatment difference (95% CI)
	Baseline mean	Endpoint Mean	Change (SE)	Baseline mean	Endpoint mean	Change (SE)	
Trial 301	36.66	NR	7.07 (0.77)	36.94	NR	6.40 (0.79)	0.67 (-1.21, 2.55)
Trial 302	42.54	NR	2.01 (0.70)	40.69	NR	0.54 (0.70)	1.47 (-0.21, 3.15)

Source: Table 55, pp115-118 of the submission, Trial 301 and 302 clinical study reports.

Abbreviations: CI, confidence interval; NR, not reported; SE, standard error.

6.15 Change from baseline in EORTC QLQ-C30 scores were included in Trials 301 and 302 as an exploratory outcome, with differences between treatment arms not assessed for non-inferiority. In Trial 301, a higher percentage of patients in the ravulizumab group had at least a 10-point improvement (suggested in the submission to be a clinically relevant change) in the Global Health Status, Physical Functioning, and Fatigue subscale scores at Day 29 and through Week 26, compared with the eculizumab group. The submission reported no noticeable change from baseline in either treatment arm of Trial 302. There was limited detail provided in the submission,

with mean baseline, endpoint and change from baseline in EORTC QLQ-C30 scores not provided, limiting the usefulness of these results. The ESC advised that the suggestion that QoL is improved by less frequent injections is not adequately supported by the PNH-specific Patient Preference Questionnaire (PNH-PPQ) included in the submission.

- 6.16 The Pre-Sub-Committee Response (PSCR) stated that the data from the PNH-PPQ suggest that the 8-weekly dosing schedule could have a significant, beneficial, long-term impact on the ability of patients to plan and lead a more normal life. However, the ESC considered that the data appeared to show no significant difference between ravulizumab and eculizumab in three out of the four reported QoL domains. Overall, the ESC considered a presumption cannot be made that less frequent infusions result in a higher QoL, despite the anecdotal accounts given.
- 6.17 Results of the meta-analysed data from Trials 301 and 302 were similar to the individual trial results for all included outcomes, with the exception of breakthrough haemolysis (Table 9 below).

Table 9: Meta-analysis results for breakthrough haemolysis

Trial	Ravulizumab n/N, (%)	Eculizumab n/N, (%)	OR (95% CI)	RR (95% CI)	RD (%) (95% CI)
Trial 301	5/125 (4.0%)	13/121 (10.7%)	0.35 (0.12, 1.00)	0.37 (0.14, 1.01)	-6.7 (-13.2, -0.2)
Trial 302	0/97 (0%)	5/98 (5.1%)	0.09 (0.00, 1.60)	0.09 (0.01, 1.64)	-5.1 (-9.8, -0.4)
Pooled result from random effects model			0.29 (0.11, 0.80)	0.32 (0.12, 0.82)	-5.7 (-9.5, -1.8)
Chi-square for heterogeneity p =, I² statistic			p=0.373, I ² =0%	p=0.356, I ² =0%	p=0.661, I ² =0%

Source: Table 89, p163 of the submission.

Abbreviations: CI, confidence intervals; OR, odds ratio; RR, relative risk; RD, risk difference

- 6.18 The meta-analysed results showed a statistically significant difference between treatment arms, with ravulizumab treated patients experiencing fewer BTH events during the trials than eculizumab treated patients. This finding forms the basis of the submission's therapeutic claim of significantly improved efficacy of ravulizumab to eculizumab on the outcome of BTH. There was a numerical difference in favour of ravulizumab in the number of BTH events, and in the number of events attributable to serum free C5 concentrations rather than other causes such as infection. However, the robustness of meta-analysis results is uncertain due to exchangeability issues between trial populations. The evaluation raised that BTH rates may not be generalisable to clinical practice as dose adjustments for eculizumab were not permitted in the trials. The ESC advised the results are likely to be generalisable to Australian clinical practice if eculizumab for PNH remains on the LSDP as dose increases are not easily accessible on the LSDP and are at the discretion of the Minister. This claim may no longer be relevant if eculizumab were subsidised on the PBS for PNH, as dose adjustments would be possible for eculizumab. The ESC also considered that the BTH results from the meta-analysis were not supported by results for other biochemical outcomes and were thus not considered reliable.
- 6.19 Results of the post-hoc subgroup analysis of 208 Trial 301 patients meeting eligibility criteria for the proposed ravulizumab restriction were consistent with the overall trial

results. All subgroup outcomes met the trial's conditions for non-inferiority. The subgroup analysis of the proportion of patients experiencing breakthrough haemolysis suggested a statistically significant difference between the ravulizumab and eculizumab treated patients (ravulizumab 3.7% vs eculizumab 12.0%, treatment difference -8.2% (95% CI -16.82, -0.37). Results must be interpreted with caution given the baseline characteristics of these patients and results of the complement for this subgroup were not provided.

- 6.20 Results of the indirect comparisons of ravulizumab and BSC were presented for the overall population, comparing the results of the meta-analysis of Trials 301 and 302, and the eculizumab TRIUMPH trial; and the treatment naïve population comparing Trial 301 with the TRIUMPH trial. The ESC considered that given exchangeability issues between the trial populations, the indirect comparison based on the meta-analysed ravulizumab trials should be interpreted with caution. Due to the limited availability of comparable outcomes, the indirect comparison was performed using three efficacy outcomes: transfusion avoidance, change in FACIT-fatigue total score, and percent change from baseline in LDH levels at Week 26.
- 6.21 Results of the indirect comparison for transfusion avoidance comparing the meta-analysed ravulizumab trials with the TRIUMPH trial, and comparing Trial 301 only with TRIUMPH, are presented in the table below.

Table 10: Indirect comparison of transfusion avoidance

Trial	Ravulizumab n/N (%)	Eculizumab n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)	RD (%) (95% CI)
TRIUMPH	–	22/43 (51.2)	0/44 (0)	93.14 (5.39, 1609.09)	46.02 (2.88, 735.53)	51.2 (36.1, 66.2)
Trial 301	92/125 (73.6)	80/121 (66.1)	–	1.43 (0.83, 2.47)	1.11 (0.94, 1.31)	7.5 (-4.0, 18.9)
Trial 302	85/97 (87.6)	81/98 (82.7)	–	1.49 (0.67, 3.31)	1.06 (0.94, 1.19)	5.0 (-5.0, 14.9)
Meta-analysis of Trials 301 and 302				1.45 (0.92, 2.27)	1.08 (0.98, 1.19)	6.1 (-1.5, 13.6)
Indirect comparison of pooled Trials 301/302 and TRIUMPH				134.8 (7.53, 2412.8)	49.6 (3.10, 794.3)	57.3 (40.4, 74.1)
Indirect comparison of Trial 301 and TRIUMPH				133.1 (7.31, 2422.2)	51.2 (3.19, 822.9)	58.6 (43.3, 74.0)

Source: Table 93, p169; Table 96, p171 of the submission.

Abbreviations: OR, odds ratio; RD, risk difference; RR, relative risk.

- 6.22 The comparison of eculizumab and placebo in the TRIUMPH trial for transfusion avoidance resulted in very wide confidence intervals, given low patient numbers in the TRIUMPH trial. Results for both indirect comparisons using pooled data from Trials 301/302 and using Trial 301 alone demonstrated a statistically significant difference in avoidance of transfusions between ravulizumab and placebo. However all measures were associated with wide confidence intervals, due to heterogeneity in the results for the common comparator arm and the low patient numbers in the TRIUMPH trial.

6.23 Results of the indirect comparison for change from baseline in FACIT-fatigue total scores comparing the meta-analysed ravulizumab trials with the TRIUMPH trial, and comparing Trial 301 only with TRIUMPH, are presented in the table below.

Table 11: Indirect comparison of change in FACIT-fatigue total scores

Trial	Ravulizumab Mean change (SD)	Eculizumab Mean change (SD)	Placebo Mean change (SD)	WMD (95% CI)
TRIUMPH	–	6.40 (7.62)	-4.0 (10.68)	10.40 (6.32, 14.48)
Trial 301	7.07 (8.64)	6.40 (8.68)	–	0.67 (-1.49, 2.83)
Trial 302	2.01 (6.86)	0.54 (6.97)	–	1.47 (-0.47, 3.41)
Meta-analysis of Trials 301 and 302				1.11 (-0.33, 2.56)
Indirect comparison of pooled Trials 301/302 and TRIUMPH				11.5 (7.2, 15.8)
Indirect comparison of Trial 301 and TRIUMPH				11.1 (6.4, 15.7)

Source: Table 94, p169; Table 96, p171 of the submission.

Abbreviations: WMD, weighted mean difference.

6.24 The indirect comparison of change in FACIT-fatigue total scores suggested a statistically significantly larger improvement in fatigue for patients treated with ravulizumab compared to placebo.

6.25 In the TRIUMPH trial report, the percent change from baseline in LDH levels was not reported. While mean percent change from baseline could be calculated using the baseline and endpoint values, it was not possible to approximate the precision associated with this change. In order to attempt an indirect comparison for LDH change, the submission conducted four comparisons, using different standard errors to fill in the missing measure of precision from the TRIUMPH trial from: treatment difference in Trial 301, treatment difference in Trial 302, pooled treatment difference, and double of the highest of the three standard errors as a conservative approach.

Table 12: Indirect comparison of % change in LDH levels

Trial	Ravulizumab Mean change (SD)	Eculizumab Mean change (SD)	Placebo Mean change (SD)	WMD (95% CI)
TRIUMPH	–	-85.12 (NR)	7.13 (NR)	-92.25 (NR)
Trial 301	-76.84 (17.69)	-76.02 (17.79)	–	-0.82 (5.25, 3.61)
Trial 302	-0.82 (29.87)	8.39 (30.10)	–	-9.21 (-17.63, -0.79)
Meta-analysis of Trials 301 and 302				-4.22 (-12.29, 3.85)
Indirect comparison of pooled Trials 301/302 and TRIUMPH, using:				
SE of treatment difference in Trial 301 (2.26)				88.0 (78.8, 97.2)
SE of treatment difference in Trial 302 (4.29)				88.0 (76.4, 99.7)
SE of pooled treatment difference from Trials 301/302 (4.12)				88.0 (76.6, 99.4)
Double of highest SE (8.59)				88.0 (69.4, 106.7)
Indirect comparison of Trial 301 and TRIUMPH, using:				
SE of treatment difference in Trial 301 (2.26)				91.4 (85.2, 97.7)
SE of treatment difference in Trial 302 (4.29)				91.4 (81.9, 100.9)
SE of pooled treatment difference from Trials 301/302 (4.12)				91.4 (82.2, 100.6)
Double of highest SE (8.59)				91.4 (74.0, 108.8)

Source: Table 95, p170; Table 96, p171 of the submission.

Abbreviations: NR, not reported; SE, standard error; WMD, weighted mean difference.

6.26 The indirect comparison of percent change in LDH levels suggested a statistically significantly larger reduction in LDH levels for patients treated with ravulizumab compared to placebo. Results of the indirect comparison demonstrated superiority of

ravulizumab over placebo, regardless of the approach used to estimate standard errors.

- 6.27 Overall, the results of the indirect comparison suggest that ravulizumab has a statistically significantly better efficacy profile than placebo for the outcomes of transfusion avoidance, percent change in LDH levels, and FACIT-fatigue scores. However, the ESC advised that the robustness of the indirect comparison was hindered by the limited number of comparable outcomes available between the trials, and issues of exchangeability between the two ravulizumab trials and the TRIUMPH trial.

Survival data

- 6.28 There are currently no long-term studies of disease progression and survival in patients treated with ravulizumab, beyond the one-year data available from the extension periods of the ravulizumab clinical trials. However, the submission argued that there is indirect evidence that ravulizumab reasonably extends the lifespan of patients with PNH, as follows:

- LDH is the established marker of haemolysis
- Raised LDH is linked to increased risk of mortality and thrombosis
- Eculizumab reduces LDH, thromboembolism risk and the risk of mortality compared to best supportive care
- Ravulizumab is non-inferior to eculizumab and binds to the same epitope of C5
- Ravulizumab will also be non-inferior to eculizumab and superior to best supportive care in reducing mortality.

- 6.29 The submission argued that LDH is a reliable, objective and direct measure of intravascular haemolysis in patients with PNH, and is considered to be the best measure of complement-mediated haemolysis, the key marker of PNH disease activity. Levels of chronic haemolysis in the eculizumab clinical trials were also measured by serum LDH. Patients with PNH with elevated haemolysis (LDH above 1.5 times the upper limit of normal) have an increased risk of experiencing thromboembolic events, the leading cause of mortality in patients with PNH. This leads to a 4.8-fold higher mortality rate for patients with PNH compared with the age- and sex-matched general population (Hillmen 2006). In 2009, the PBAC stated the “link between treatment with eculizumab resulting in the reduction of thromboembolic events and an improved lifespan of some patients with PNH was not unreasonable” (Section 12, Public Summary Document, eculizumab, March 2009). The ESC considered this conclusion should be re-examined taking into account the variation in the results for improved survival from more recent evidence.

- 6.30 In the July 2010 PBAC submission for eculizumab, survival data from the eculizumab clinical trials (SHEPHERD and E05-001 extension study) was compared to a matched PNH patient cohort from 1996-2005 (de Latour 2008), with the conclusion that eculizumab treatment significantly reduced mortality (82% reduction, observed vs expected deaths). The PBAC deferred the submission for eculizumab to allow the

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sponsor time to obtain further data about the magnitude of the survival gain before making a decision on whether eculizumab substantially extends a patient’s lifespan as per criterion 4 of the Life Saving Drugs Program (para 11, eculizumab, July 2010 Public Summary Document). In August 2010 the PBAC considered that the additional evidence, including that presented by the sponsor and unpublished data, acceptably supported the prediction that a patient’s lifespan with classic PNH would be substantially extended as a direct consequence of treatment with eculizumab compared to best supportive care and hence concluded that criterion four of the LSDP was now met (August 2010 addendum, eculizumab, July 2010 Public Summary Document).

Table 13: Survival data previously considered by the PBAC for eculizumab (August 2010), three-year mortality rate for best supportive care in 1996 – 2005 vs Eculizumab

Expected Mortality with Best Supportive Care (de Latour 2008)		Eculizumab trials (SHEPHERD, E05-001 extension study), N=195		Odds ratio (95% CI), p-value ^b
3 yr Observed Mortality Rate	Expected Deaths Applied to N=195 ^a	Observed Deaths	% Reduction	
12.1%	24	4	82%	0.15 (0.05 -0.44), p<0.0001

^aNumber of deaths expected during three years were estimated by multiplying the rate of expected mortality (de Latour et al., 2008) over three years by the number of patients enrolled in the eculizumab trials.

^bp value based on Pearson’s chi-squared test. Source: Table 107, p 192 of the submission.

6.31 The submission included a number of clinical studies, retrospective analyses and registry studies that have been published since the PBAC consideration of eculizumab, which include information on disease progression and survival for patients treated with eculizumab or BSC (see table below).

Table 14: Updated survival data for eculizumab (published after July 2010 eculizumab submission)

Source	Patients (N)	Age at diagnosis, years, median (range)	Diagnostic test used	Data collection (Year range)	Duration of follow up, years, median (range)	Survival	
						% alive (95% CI)	Survival timepoint, years
Best supportive care							
Kelly 2011 (UK)	30 ^a	NR	NR	1997-2004	7 (NR)	66.8 (41.4, 85.1)	5
Munoz-Linares 2014 (Spain) ^b	56	32.8 (IQR 13-84)	<1994 Ham >1994 FC	1970-2013	11.4 (NR)	Median survival 11 years	
Loschi 2016 (France)	100 ^c 191	38 (26-51) 38 (27-50)	Ham and/or FC	>1985 1954-1985	5.1 (1.8-11.4) 9.4 (2.2-15.9)	80 (70, 91) 58 (48, 70)	6 6
Hill 2017 (International)	3058 ^d	44.8 (at baseline)	FC	2016	Mean 32.1 (SD 25.0) months	Mortality rate 2.19 (1.83, 2.63) per 100 patient-yrs	
Ecuzumab							
Kelly 2011 (UK)	79	37 (12-79)	FC	2002-2012	8 (NR)	95.5 (87.6, 98.5)	5
Hill 2012 (UK)	153	34 (12-80)	FC	2002-2012	10 (NR)	94 (NR)	10
Hillmen 2013 (International)	195	39.7 (18-85)	FC	NR	5.5 (NR)	97.6 (93.8, 99.1)	3 and 5.5
Loschi 2016 (France)	123	37 (24-49)	FC	2005-2014	4.5 (2.5-5.6)	92 (87, 98)	6
Munoz-Linares 2014 (Spain) ^b	16	32.8 (IQR 13-84)	FC	1970-2013	3 months – 6 years	NR	
Jang 2016 (Korea)	301	37 (8-88)	Ham and/or FC	2009-2010	6.6 (0-28.8)	SMR 3.89% (2.73, 5.05) vs age/sex matched general population	
Socie 2016 ^e (International)	2356	NR	FC	2014	9.4 (NR)	94.8 (NR) 93.3 (NR)	10 15
Hill 2017 (International)	1587 ^d	43.4 (at baseline)	FC	2016	Mean 50.0 (SD 30.9) months	Mortality rate 1.13 (0.89, 1.42) per 100 patient-yrs	

Source: Table 109, pp195-196 of the submission, relevant publications

Abbreviations: FC, flow cytometry; IQR, interquartile range; NR, not reported; Retro, retrospective; SD, standard deviation; SMR, standard mortality ratio

Note: Data presented in the submission from Hillmen 1995, Socie 1996, Moyo 2004, Nishimura 2004 and de Latour 2008 were omitted from this table as mortality data from these studies have already been considered by the PBAC in the previous ecuzumab submissions.

^a Kelly 2011 – the 30 'control' patients were a subgroup of the total study patient group, who were assessed as controls, up to the point that they commenced treatment with ecuzumab.

^b Munoz-Linares 2014 – 16 of the 56 patients included in this review were treated with ecuzumab with follow-up ranging from 3 months to 6 years. Survival data were not reported separately for this patient subgroup.

^c Loschi 2016 – the 100 patients diagnosed after 1985 were a subgroup of the 191 historical controls.

^d Hill 2017 – 1587 patients were treated with ecuzumab at the time of enrolment in the registry, 3058 were not treated with ecuzumab; with 632 patients contributing time to both groups.

^e Socie 2016 – not all registry patients were treated with ecuzumab. 28.7% were treated with ecuzumab on enrolment with the registry, and 46.4% were treated with ecuzumab during the follow up period. Mortality was not reported separately based on treatment, however in an adjusted model, ecuzumab was associated with significantly better survival outcome as a time-dependent factor.

6.32 Despite the updated publication dates for studies incorporating BSC data, there were limited data available and the timeframes for data collection in many of the studies is still quite dated. Results from Loschi (2016), in which the proportion of surviving patients at 6 years follow-up was greater for patients after 1985, compared to patients

diagnosed between 1954 to 1985, were consistent with the idea that best supportive care survival (overall disease management of thromboses with better treatment, earlier diagnosis, better diagnosis of concomitant bone marrow disorders) has improved over time. However, given the established place of eculizumab in treating PNH, it is unlikely that the body of evidence for survival with BSC will improve.

- 6.33 The updated eculizumab survival data are in line with previously reported rates of survival, and the submission suggests that mortality rates are at a similar level to that of the general population (based on data from Kelly 2011). However, the follow-up durations of these studies were relatively short given the median age of patients at diagnosis, and a lack of useful comparative data means that it is difficult to determine the magnitude of any survival benefit for eculizumab.
- 6.34 The ESC also noted that new data for eculizumab provided by the Sponsor on 5 June 2020 (included in the agenda for ravulizumab as a supplementary document named 'Attachment 1, Solaris minor submission response'), re-presented the survival advantage with eculizumab versus BSC including more recent patient cohorts than previously considered by PBAC, with BSC survival ranging from 66.8% (Kelly 2011) to 88.7% (de Latour 2008). However, the ESC considered the availability of new and different data provided across multiple communications relating to ravulizumab and eculizumab — the ravulizumab submission, LSDP Review for eculizumab and minor submission response correspondence for eculizumab — confounded the interpretation of the information presented in this submission.

Comparative harms

- 6.35 A summary of key adverse events for the included trials is presented in Table 13. All patients in the included clinical trials received a meningococcal vaccine before commencing study drug treatment and no meningococcal infections were reported in any of the treatment arms of the trials.

Table 15: Summary of key adverse events in the randomised trials

Adverse event type	Trial 301		Trial 302		TRIUMPH	
	RAV n (%) N=125	ECU n (%) N=121	RAV n (%) N=97	ECU n (%) N=98	ECU n (%) N=43	PLACEBO n (%) N=44
Any AE	110 (88.0)	105 (86.8)	85 (87.6)	86 (87.8)	43 (100)	40 (90.9)
Treatment-emergent SAE	11 (8.8)	9 (7.4)	4 (4.1)	8 (8.2)	4 (9.3)	9 (20.5)
Deaths	0 (0)	1 (0.8) ^a	0 (0)	0 (0)	0 (0)	0 (0)
AE leading to withdrawal	0 (0)	1 (0.8) ^a	0 (0)	0 (0)	1 (2.3)	0 (0)
AE related to study drug ^b	51 (40.8)	50 (41.3)	24 (24.7)	14 (14.3)	24 (55.8)	11 (25.0)
SAE related to study drug ^b	4 (3.2)	1 (0.8)	1 (1.0)	1 (1.0)	0 (0)	1 (2.3)
Grade 3+ severe AEs	26 (20.8)	22 (18.2)	9 (9.3)	14 (14.3)	NR	NR
Adverse events of special interest						
Meningococcal infections	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Aspergillus infections	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR
Other serious infections	2 (1.6)	4 (3.3)	2 (2.1)	1 (1.0)	0 (0)	4 (9.1)
Sepsis	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR
Infusion reactions	11 (8.8)	10 (8.3)	8 (8.2)	3 (3.1)	0 (0)	1 (2.3)
Serious cutaneous AEs	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR
Cardiac disorders	2 (1.6)	0 (0)	0 (0)	1 (1.0)	2 (4.7)	0 (0)
Angioedema	3 (2.4)	0 (0)	1 (1.0)	0 (0)	NR	NR

Source: Table 75, pp148-149; Table 77, pp151-152; Table 79, pp154-155 of the submission; Trial 301 and 302 clinical study reports.

Abbreviations: AE, adverse event; ECU, eculizumab; n, number of participants reporting data; N, total participants in group; NR, not reported; RAV, ravulizumab; SAE, serious adverse events.

^a Patient withdrew during extension period of trial. Adverse event and death (lung cancer) was not attributable to the study drug.

^b classed as definitely, probably, or possibly related to study drug.

6.36 In Trial 301, adverse events were similar across treatment arms, with headache (36% versus 33% for ravulizumab and eculizumab, respectively), upper respiratory tract infections (22% vs 36%) and pyrexia (5% vs 11%) the most frequently reported adverse events. There were no adverse events leading to withdrawal or death during the primary evaluation period. One eculizumab-treated patient withdrew during the extension period of the trial and subsequently died from an unrelated condition (lung cancer). In Trial 302, the most frequently reported adverse events were headache (27% versus 17% for ravulizumab and eculizumab, respectively), nasopharyngitis (22% vs 20%) and upper respiratory tract infections (19% vs 10%). The percentage of patients with adverse events assessed as related to the study drug was higher in the ravulizumab group than in the eculizumab group (24.7% vs 14.3%). No patients died and no patients discontinued from the study due to adverse events during the primary evaluation period. The results from the ravulizumab trials suggested that ravulizumab has a similar safety profile to eculizumab.

6.37 In the TRIUMPH trial, the most frequently reported adverse events were headaches (44% vs 27% of eculizumab and placebo treated patients, respectively), nasopharyngitis (23% vs 18%), upper respiratory tract infection (14% vs 23%) and back pain (19% vs 9%). Fatigue was reported by more eculizumab-treated patients (11.6%) than placebo treated patients (2.3%). One eculizumab patient withdrew from the trial due to pregnancy. There were no deaths during the study. The submission did not present an indirect comparison of safety between ravulizumab and best supportive

care, but assumed that the likely inferiority of eculizumab to best supportive care in terms of safety would also apply to ravulizumab. Given the similar mechanism of action between ravulizumab and eculizumab, and similar patterns of adverse events reported in the ravulizumab and eculizumab trials, the ESC considered this assumption was reasonable.

- 6.38 An expanded assessment of harms identified important risks including meningococcal infection, which is directly associated with ravulizumab's mode of action. However, long-term post marketing experience with eculizumab shows stable overall reporting rates of meningococcal infections (0.3-0.5 per 100 patient years), suggesting risk minimisation measures (meningococcal vaccination) appear to be appropriate and effective in reducing this risk. Important potential risks include serious haemolysis after drug discontinuation in PNH patients, immunogenicity, serious infections and malignancies and hematologic abnormalities in PNH patients. There is no information available on use in pregnant and breast-feeding women.

Benefits/harms

- 6.39 A benefits/harms summary for the comparison of ravulizumab and eculizumab was not presented as the clinical claim was based on non-inferiority. The submission's claim of superior efficacy for ravulizumab to eculizumab for the outcome of breakthrough haemolysis relied on a meta-analysis of the two ravulizumab trials that may not be appropriate given differences in the trial populations (treatment-naïve vs treatment experienced). Further, the generalisability of these results to the PBS population is uncertain given that no adjustments of up to 2 days (or a higher dose) were permitted in the trials for eculizumab-treated patients to manage breakthrough haemolysis.
- 6.40 A benefits/harms summary for the comparison of ravulizumab and best supportive care was not presented as current data are inadequate to reliably quantify the comparative benefits and harms of ravulizumab and best supportive care.

Clinical claim

- 6.41 The submission described ravulizumab, administered every 8 weeks, as non-inferior in terms of effectiveness and non-inferior in terms of safety compared to eculizumab, administered every 2 weeks; but that ravulizumab is superior in terms of reduction in risk of breakthrough haemolysis compared to eculizumab.
- 6.42 The ESC agreed with the clinical claim that ravulizumab, administered every 8 weeks, and was likely to be non-inferior based on surrogate outcomes and safety compared to eculizumab.
- 6.43 The therapeutic conclusion of superior efficacy for ravulizumab in terms of reduction in the risk of breakthrough haemolysis was based on the meta-analysis of Trials 301 and 302, which may not be appropriate given differences in the trial populations (treatment-naïve vs treatment experienced). These trials were powered to test non-inferiority based on the primary outcomes (transfusion avoidance and LDH

normalisation in Trial 301, and percent change in LDH from baseline in Trial 301). The individual trials may not have had sufficient power to detect a statistically significant difference between ravulizumab and eculizumab in terms of breakthrough haemolysis. There was a numerical difference in favour of ravulizumab in the number of BTH events, and in the number of events attributable to serum free C5 concentrations rather than other causes such as infection. However, the evaluation suggested generalisability of these results to the PBS population is uncertain given eculizumab treatment was given every 14 days in Trials 301 and 302, meaning that there were no adjustments of up to 2 days (or a higher dose) permitted to manage breakthrough haemolysis. The ESC considered the results are likely to be generalisable to Australian clinical practice if eculizumab for PNH remains on the LSDP as dose increases are not easily accessible on the LSDP and are at the discretion of the Minister. However, this claim may no longer be relevant if eculizumab were subsidised on the PBS for PNH, as dose adjustments would be possible for eculizumab.

- 6.44 The ESC noted there was no significant difference in the clinical outcomes reported in any of the individual clinical trials (Table 7) and the reported clinically significant difference in BTH was based on the meta-analysis of Trials 301 and 302.
- 6.45 The ESC advised BTH alone, marked by an increase in LDH levels is not clinically significant unless it is associated with other clinical features such as fatigue and the requirement for transfusion. The ESC considered transfusion avoidance, reduction in microthrombosis, macrothrombosis and stabilisation of haemoglobin levels are more clinically significant outcomes than BTH measured by LDH stabilisation.
- 6.46 Given the reduced clinical significance of BTH compared to other clinically meaningful outcomes and the uncertainty of the robustness of the meta-analysed results, the ESC considered that ravulizumab was non-inferior in regards to BTH to eculizumab.
- 6.47 The submission described ravulizumab as superior in terms of effectiveness and inferior in terms of safety compared to best supportive care. The ESC noted the clinical claim against BSC was indirect, made via a comparison of eculizumab with BSC. The robustness of the indirect comparison was hindered by the limited number of comparable outcomes available between the trials, and issues of exchangeability between the ravulizumab trials and the TRIUMPH trial. However, given ravulizumab is a pharmacological analogue of eculizumab, and results of the direct comparison with eculizumab suggest non-inferior efficacy of ravulizumab to eculizumab, the ESC considered it may be reasonable to assume superior efficacy of ravulizumab to BSC in terms of the outcomes reported (transfusion avoidance, change in FACIT-fatigue total score, and percent change from baseline in LDH levels at Week 26).
- 6.48 However, it may not be reasonable to assume that the superior survival benefit previously accepted for eculizumab compared to BSC can be applied to ravulizumab compared to best supportive care, in the absence of any long term survival data for ravulizumab. Moreover, the magnitude of any survival benefit of eculizumab

compared to BSC is itself unclear, given the lack of contemporary data for BSC survival outcomes.

- 6.49 The therapeutic conclusion of inferior safety of ravulizumab to BSC was based on an assumption that the likely inferiority of eculizumab to BSC in terms of safety would also apply to ravulizumab. Given the similar mechanism of action between ravulizumab and eculizumab, and similar patterns of adverse events reported in the ravulizumab and eculizumab trials, this assumption was reasonable.
- 6.50 The PBAC considered that the claim of superior comparative effectiveness compared to BSC and non-inferior comparative effectiveness to eculizumab was reasonable, although it was uncertain whether a patient's lifespan would be substantially extended as a direct consequence of the use of ravulizumab.
- 6.51 The PBAC considered the claim of inferior safety compared to BSC and non-inferior safety compared to eculizumab was reasonable.

Economic analysis

- 6.52 The submission presented two cost-utility analyses; one comparing ravulizumab with eculizumab and another comparing ravulizumab (using eculizumab as a proxy) with best supportive care. These analyses are presented in their respective sub-sections below.
- 6.53 The PBAC previously rejected listing eculizumab on the PBS on the basis of an unacceptably high and highly uncertain cost-effectiveness (eculizumab PSD, March 2009 PBAC meeting). Eculizumab was recommended for inclusion on the LSDP in August 2010 (eculizumab PBAC PSD, addendum to July 2010 PBAC meeting).
- 6.54 The comparison with eculizumab was used to establish the requested price for ravulizumab (used in the best supportive care model). The requested price was calculated based on [REDACTED] associated with the claimed benefits. The ESC noted that this had implications on the economic analysis of the submission, given eculizumab is not PBS-listed.
- 6.55 The comparison with BSC was used to establish the cost-effectiveness of ravulizumab for listing on the PBS.

Ravulizumab versus eculizumab

- 6.56 The submission presented a simple decision-tree analysis to estimate improved quality of life driven by reduced infusions and rates of breakthrough haemolysis, as well as reduced administration costs when comparing ravulizumab with eculizumab over 1 year.

Table 16: Key components of the economic evaluation

Component	Description
Type of analysis	Cost utility analysis
Outcomes	Cost per infusion avoided, cost per day of BTH avoided, QALYs
Time horizon	1 year
Methods used to generate results	Decision tree analysis
Costs	Ravulizumab drug (█ vials per year, \$█ per vial) and administration cost (\$99.50, 6.5 infusions per year). Number of vials required estimated using weight distributions from the key ravulizumab trial, 301, and recommended doses every 8 weeks (40 to <60 kg: █% at 3,000 mg, 60 to <100 kg: █% at 3,300 mg, 100+ kg: █% at 3,600 mg). Eculizumab drug (█ vials per year, \$█ per vial) and administration cost (\$66.10, 26 infusions per year). Number of vials required estimated based on the recommended dose of 900 mg at a fixed 2-weekly dosing interval.
Health related quality of life	Baseline PNH utility (0.7470) Non-specific disease-related utility gain (0.1020) BTH disutility (-0.1828) Increased infusion frequency disutility (-0.058)
Modelled outcomes	Number of infusions avoided based on frequency of administration of ravulizumab (8-weekly) versus eculizumab (fixed 2-weekly) Days of BTH avoided based on the key trials 301 and 302 and assumptions

Source: Table 111, p 241 of the submission

Abbreviations: BTH, breakthrough haemolysis; PNH, paroxysmal nocturnal haemoglobinuria; QALY, quality adjusted life year

- 6.57 The dosing equivalence of ravulizumab and eculizumab was calculated based on recommended doses. Ravulizumab dosing is weight-based, with heavier patients being administered higher doses whereas eculizumab dosing is irrespective of weight.
- 6.58 The submission assumed weight distributions from Trial 301 are applicable to the Australian population. This assumption was inadequately justified. Weight distributions from other sources (Trial 302 and Australian PNH registry patients) suggest that there may be more patients in higher weight categories in the PBS population compared with the Trial 301 population.
- 6.59 Drug costs for ravulizumab (█ vials) and eculizumab (█ vials) were calculated based on the number of vials in the average maintenance year. The submission claimed the PBAC Guidelines recommend the use of maintenance doses only for costing purposes. The Guidelines were referring to cost-minimisation analyses. The estimated number of vials required during the initiation year for ravulizumab (█ vials) is similar to the required eculizumab vials for the same period (█ vials). Consequently, the drug cost for ravulizumab (using a requested price based on the maintenance phase) is higher compared to eculizumab in the initial year.
- 6.60 The cost of eculizumab in the model does not incorporate the 10% statutory price reduction. This was inconsistent with the estimated cost of eculizumab used in the budget impact model and results in a higher cost per patient for ravulizumab compared with eculizumab after April 2021.
- 6.61 The claimed benefits and reduced cost associated with ravulizumab versus eculizumab when assuming pricing parity resulted in █ (Table 17).

Table 17: Results of the economic evaluation

Component	Ravulizumab	Eculizumab	Increment
Costs			
QALYs	0.8488	0.7889	0.0600
Incremental cost/QALY gained			

Source: 'Attachment 6A. Ultomiris vs Soliris CE – Excel' of the submission

Abbreviation: QALY, quality adjusted life years

6.62 These results should not be considered reliable due to concerns with the modelled outcomes:

- QALYs associated with infusions were dependent on a highly uncertain disutility value due to major concerns with the robustness of the discrete choice experiment and approach used to map preferences to utility values; and
- There was inadequate justification for the inclusion for BTH events in the model given the claim of fewer BTH events with ravulizumab versus eculizumab was not adequately supported.

Ravulizumab (using eculizumab as a proxy) versus BSC

6.63 The ESC noted the substantial uncertainty in the modelled economic analyses, and considered the model structure used in the comparison versus BSC lacked face validity and was unlikely to be helpful for decision making.

6.64 The submission presented a stepped economic evaluation of ravulizumab (using eculizumab as a proxy) compared with BSC (using historical control as a proxy) for the treatment of paroxysmal nocturnal haemoglobinuria (PNH). The economic model was based on extrapolated survival curves from a retrospective observational study of patients with PNH and other modelled variables.

Table 18: Key components of the economic evaluation

Component	Description
Type of analysis	Cost utility analysis
Outcomes	QALYs
Time horizon	55 years in the model base case versus a maximum of 8 years follow-up in the retrospective observational study (Kelly 2011)
Methods used to generate results	Hybrid partitioned survival analysis/Markov cohort model
Health states	Alive with PNH Alive in remission Dead
Cycle length	1 year
Transition probabilities	Separately modelled overall survival curves for ravulizumab (using eculizumab as a proxy) and BSC (using historical control as a proxy) using parametric distributions over the whole model duration. Models were based on reconstructed Kaplan-Meier curves from the Kelly 2011 retrospective study by digitisation of published figures and assumptions. The ESC considered the applicability of the Kelly 2011 retrospective study to represent contemporary BSC was unclear and likely underestimated survival in the BSC arm. A survival cap was included based on age-adjusted mortality in the Australian population. A spontaneous remission transition probability was derived from a natural history study of PNH based on 80 patients in a UK hospital between 1940 and 1970 (Hillmen 1995). The

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Component	Description
	<p>probability of death in the alive in remission health state was based on age-adjusted general population mortality in the Australian population).</p> <p>83% of incremental life years (alive with PNH), 98% of incremental life years (alive in remission), 75% of incremental QALYs and 54% of incremental costs are accrued in the extrapolated period.</p>
Health related quality of life	<p>Baseline PNH utility (both arms): 0.7559 Ravulizumab non-specific disease-related utility gain: 0.1012 BSC non-specific disease-related disutility: -0.0610 Thromboembolic events disutility (distributed across treatment arms using rates of thromboembolic events derived from Kelly 2011 and assumptions): -0.0750 Ravulizumab reduced infusion frequency utility gain: 0.0580</p> <p>Utility data were based on quality of life scores (EORTC QLQ-C30) from TRIUMPH and SHEPHERD eculizumab studies mapped to utility values (EQ-5D-3L), published estimates (Lloyd 2018, Lloyd 2019 unpublished discrete choice experiment, Szende 2014) and assumptions. Utility values were capped in the ravulizumab arm to reflect the utility value of the general population.</p>
Health resource use and costs	<p>Ravulizumab drug costs were estimated using the requested price of ravulizumab (\$ [redacted] per vial) and estimated vial use based on trial-based weight distributions ([redacted] initial year, [redacted] subsequent years). Administration costs were based on the cost of an IV infusion for 2 hours or more (\$99.50) and number of infusions per year (8 initial year, 6.5 subsequent years). Meningococcal vaccine one-off drug costs of \$71.45.</p> <p>RBC transfusion costs were estimated based on the manufacturing cost per blood bag (\$402) and MBS procedure cost (\$121) and an estimated number of transfusions in the ravulizumab (5.0 per year) and BSC (19.3 per year) arms from the Kelly 2011 retrospective study.</p> <p>The cost of specialist visits was based on MBS consultation costs an assumed number of visits per year (\$221 initial year, \$177 subsequent years). Anticoagulation costs were calculated as an average annual cost based on warfarin/rivaroxaban (\$757 per year).</p> <p>All costs were only attributed to patients remaining in the alive with PNH health state.</p>

Source: Table 111, p 241 of the submission

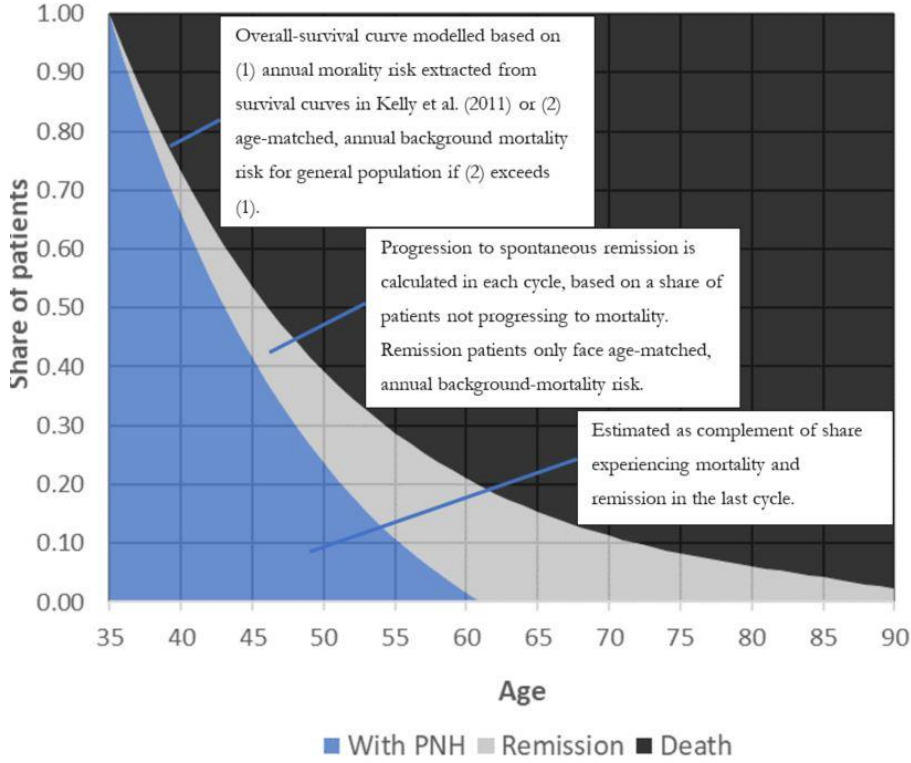
Abbreviations: BSC, best supportive care; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-3L, EuroQol 5-dimension 3-level quality of life questionnaire; PNH, paroxysmal nocturnal haemoglobinuria; QALY, quality adjusted life year; RBC, red blood cell.

6.65 A hybrid partitioned survival/Markov cohort design was used to distribute patients between health states in the model. The modelled overall survival curves for ravulizumab and BSC, and a transition probability for spontaneous remission were used to distribute patients between the model health states:

- Alive with PNH – based on the area below the overall survival curve minus patients in the alive in remission health state;
- Alive in remission – based on the spontaneous remission transition probability applied to the proportion remaining in the alive with PNH health state. Patients in this health state can also progress to death due to background mortality; and
- Dead – based on the area above the overall survival curve.

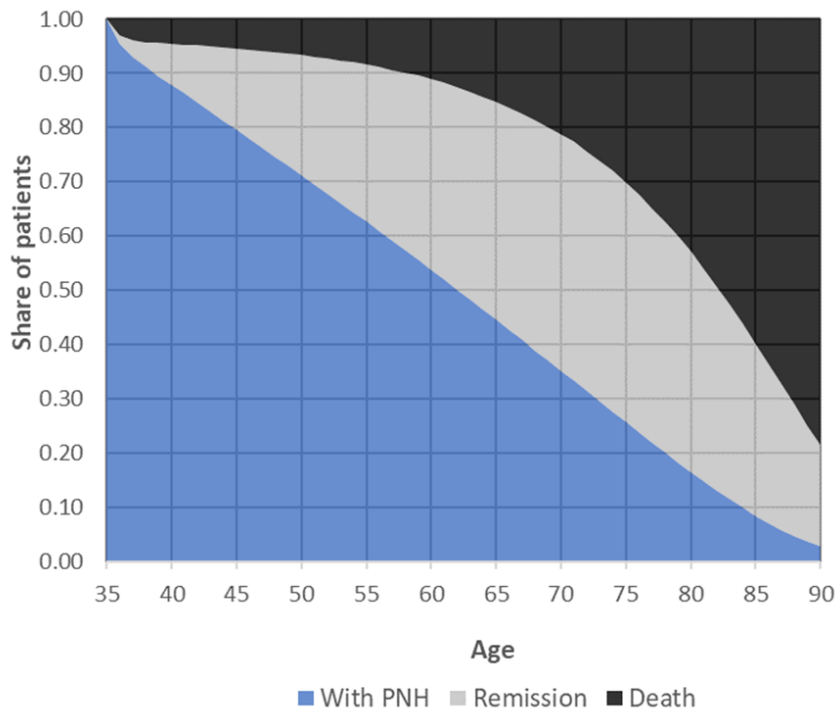
6.66 The relationship between survival curves and health states in the economic model is illustrated in the figures below.

Figure 1: Proportion of patients in each health state based on the BSC arm



Source: Figure 56, p 244 of the submission

Figure 2: Proportion of patients in each health state based on the ravulizumab arm



Source: Figure 57, p 245 of the submission

- 6.67 Due to model structure, there was no explicit relationship between treatment effect, the risk of thromboembolic events, blood transfusions and overall survival. This approach may be reasonable in instances where the relationship between these components is fully preserved (e.g. data informing the modelled components is fully captured over the model duration). However, there was considerable uncertainty with the robustness of the comparison between eculizumab and a historical cohort that formed the basis of model inputs in the first 8 years of the model and additional concerns with the reliability of modelled survival curves over the 55 year duration.
- 6.68 There was added structural uncertainty due to the inclusion of a spontaneous remission health state within a partitioned survival analysis. A correction in the model was required to ensure that the model meets face validity. Beyond Year 27 in the model, the proportion of patients in the alive in remission health state exceeds the overall survival curve in the BSC arm of the model. The base case was revised during the evaluation with the inclusion of a correction for deaths.
- 6.69 The inclusion of a reduced infusion frequency utility gain in patients treated with ravulizumab was inappropriate, as this is a comparison against BSC.
- 6.70 The submission used data from the Kelly (2011) study of PNH patients treated with eculizumab to estimate the rate of thromboembolic (TE) events in the economic model. There were concerns with the reliability of rates of TE events based on the Kelly (2011) study given the same study sample was used to determine the rates before and after eculizumab treatment. There is potential for survivor bias as well as confounding due to changes in anticoagulation management over time, particularly in patients experiencing a prior event. The submission did not adequately justify the use of an incidence estimate as the rate of events in the BSC arm, or the inappropriate calculation of a rate estimate for ravulizumab using a rate ratio and an incidence.
- 6.71 Transfusion costs are likely to be overestimated as they were based on transfusion requirements from an older, retrospective observational study that was unlikely to be applicable to the PBS population (Kelly 2011). Data from the key trials suggest considerably lower transfusion requirements with best supportive care, and smaller numbers of transfusions avoided with ravulizumab treatment. The submission inappropriately assumed that each unit of blood represented one transfusion.
- 6.72 To estimate ravulizumab drug costs, the submission assumed weight distributions from Trial 301 are applicable to the Australian population. This assumption was inadequately justified. Weight distributions from other sources (Trial 302 and Australian PNH registry patients) suggest that there may be more patients in higher weight categories in the PBS population compared with the Trial 301 population.
- 6.73 Key drivers of the economic model are summarised in the table below.

Table 19: Key drivers of the model

Description	Method/Value	Impact
Modelled survival	Kaplan-Meier survival curves for ravulizumab and BSC based on a retrospective	High, favours

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Description	Method/Value	Impact
	<p>observational study of patients treated with ecuzumab (N=79, mean treatment duration 3.3 years) compared with a matched historical control group (N=30, 7-year look-back period prior to ecuzumab availability) (Kelly 2011).</p> <p>The results suggest a reduction in risk of mortality in patients treated with ecuzumab versus patients who did not receive ecuzumab treatment (HR 0.21, 95% CI: 0.05, 0.88). The 5-year survival rate for patients treated with ecuzumab was 95.5% (95% CI: 87.6%, 98.5%) compared to 66.8% (95% CI: 41.4%, 85.1%) who did not receive ecuzumab. These results should be interpreted with caution given the wide confidence intervals (particularly for survival rates in the pre-ecuzumab group) and the nature of the non-randomised comparison that may be subject to confounding. There is a likelihood of survivor bias as some patients in the ecuzumab group acted as their own controls. There was added uncertainty in the robustness of the comparison due to limited reporting (e.g. year of diagnosis unreported, no disaggregated data by type of PNH, no justification for 7-year look-back period for the historical control, number and cause of deaths in historical control not reported, patient and disease characteristics for historical control not reported).</p> <p>Data were reconstructed in the submission using digitisation of published figures, assumed time at risk (as numbers at risk were not reported in the publication) and assumed timings of censoring and death. Overall, the reliability of reconstructed data used in the submission is highly uncertain given concerns with the robustness and applicability of survival data from the Kelly 2011. There were further concerns with the assumptions used in the submission to estimate the number of patients remaining at risk (and consequently, time at risk in the regression models) that introduced further uncertainty with the survival estimates used in the economic evaluation</p> <p>Overall survival for ravuzumab (using ecuzumab as a proxy) was modelled to 55 years using a Gompertz (proportional hazards) curve. Overall survival for BSC (using historical control) was modelled to 55 years using an exponential (accelerated time failure) curve. The submission did not provide justification for the use of modelled data only, which is inconsistent with the PBAC Guidelines v5.0 recommending the use of observed time to event data up to the time point at which the observed data become unreliable as a result of small number of patients remaining event-free. Based on visual inspection, there is an apparent divergence between the Kaplan-Meier survival curve for best supportive care and the various parametric distributions (see Figure 3 below). The submission did not provide adequate justification for the choice of survival models aside from AIC and BIC statistical values. The modelled survival curve for BSC using the exponential distribution (accelerated failure time model) assumes an accelerated reduction in life expectancy whereas the choice of a Gompertz (proportional hazards) model for the ravuzumab arm assumes constant hazards over time. Consequently, this approach generates a substantial mortality gain with ravuzumab treatment compared to BSC over the 55-year model duration. The ESC considered the chosen extrapolation functions were not adequately justified and resulted in optimistic survival gain over 55 years compared to published studies (see Figure 5 below).</p>	ravuzumab
Background mortality	<p>Based on the Australian Bureau of Statistics (ABS) 2012-2014 life tables. The background mortality rate was used in the model as a survival cap to ensure that the proportion remaining alive with PNH did not exceed general population survival estimates. The background mortality was also applied to all patients in the alive with remission health state.</p> <p>Beyond Year 5 in the model, the survival cap was applied to the ravuzumab arm</p>	High, favours ravuzumab

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Description	Method/Value	Impact
	<p>because the modelled survival function generated estimates that exceeded survival in the general population. This assumes that after 5 years of treatment, all patients with PNH who are treated with ravulizumab have the same mortality rate as the general population (see Figure 4 below). The ESC considered the requirement for a cap suggests the model is not capturing survival appropriately. The submission claimed that this was supported by a comparison of survival between eculizumab treated patients compared to age- and sex-matched controls from the UK population (Kelly 2011). The robustness of these results was uncertain given limitations in the reporting of the study (e.g. numbers at risk and reasons for censoring unreported). A comparison of age at diagnosis (median 37, range 12-79 years) and age at the start of eculizumab (median 46, range 14-84 years) suggests a considerable time lag between diagnosis and initiation of eculizumab, which may contribute to the potential for survivor bias. The survival data in eculizumab-treated patients in this study was immature (mean treatment duration 3.3 years) and may not represent long-term mortality in patients who still have PNH.</p>	
<p>Spontaneous remission transition probability</p>	<p>Annual transition probability of 0.0158. Natural history study of PNH based on 80 patients referred to a UK hospital between 1940 and 1970 who were followed up until 1994 (Hillmen 1995). Patients were treated with supportive measures only (e.g. anticoagulation, transfusions). The Hillmen 1995 study may not be applicable to the current setting given the age of the data due to changes in diagnostic methods and disease management over time. The ESC questioned the applicability of this data to the current setting, given the age of the data and potential changes to diagnostic methods and disease management over time.</p> <p>Patient-level data were estimated based on Figure 1 in the publication, following the disease course of individuals (onset of symptoms, background of aplastic anaemia, positive Ham's test, clinical cure and negative Ham's test) and assumed periods at risk (timing of death, censoring and remission are rounded to nearest 5-year increment except for duration <5 years which are rounded to 1 year). Patients who experienced both a clinical cure and negative Ham's test were assumed to achieve remission at the time of clinical cure. The submission conducted a regression analysis using the extracted data to estimate the rate of spontaneous remission over time and this was converted to an annual probability. The estimated rate of spontaneous remission may not be reliable given the use of data extracted from published figures and multiple assumptions used to determine follow-up durations and timings of death, censoring and remission.</p> <p>Overall, the occurrence of spontaneous remission appears to be confounded by changes in diagnostic methods, overlapping conditions (e.g. aplastic anaemia) and the development of other conditions (e.g. myelodysplastic syndrome, leukaemia). The rate of spontaneous remission in classic PNH patients is unclear but likely to be small given the use of modern assays and clinical criteria in the proposed restriction (combination of biomarkers and clinical symptoms).</p> <p>The application of a fixed transition probability to both arms in the model biased the results in favour of ravulizumab due to mortality benefit associated with ravulizumab (i.e. greater proportion of patients remaining alive in the ravulizumab arm who achieve spontaneous remission and accrue no ongoing costs or consequences).</p>	<p>High, favours ravulizumab</p>
<p>Non-specific disease-related utility change</p>	<p>The submission claimed that treatment with ravulizumab is associated with improvements with disease outcomes such as fatigue, pain and dyspnoea (which are independent of a reduced risk of thromboembolic events) that would translate to non-specific disease-related quality of life changes. The submission claimed that the improvement in these symptoms could be attributed to a reduction in intravascular haemolysis associated with treatment. Both FACIT-fatigue and EORTC QLQ-C30</p>	<p>High, favours ravulizumab</p>

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Description	Method/Value	Impact
	<p>results from Trial 301 suggest an improvement in measures of fatigue from baseline to 26 weeks. <i>The ESC noted the claimed improvements in other domains could not be validated during the evaluation as there was limited detail provided in the submission (no baseline, endpoint and change in baseline for EORTC QLQ-C30 scores). Additional data provided in the PSCR suggest no detectable difference in quality of life between patients treated with ravulizumab and eculizumab based on EORTC-QLQ-C30 scores.</i></p> <p>The utility gain applied to ravulizumab (0.1012) was based on a calculated difference between a synthesised EQ-5D-3L utility value at 52 weeks (0.8486) and baseline utility value (0.7474). The disutility applied to BSC (-0.0610) was based on a calculated difference between estimated 26-week utility values for placebo patients in the TRIUMPH trial (0.7254) and the estimated baseline utility for PNH (0.7559).</p> <p>The estimated non-specific disease-related utility changes were highly uncertain due to the following reasons:</p> <ul style="list-style-type: none"> • The derivation of a non-specific disease-related utility gain associated with ravulizumab treatment was complex and difficult to interpret given the use of synthesised EORTC QLQ-C30 scores from multiple datasets and the use of mapping algorithms based on cancer conditions that have not been validated for PNH. • A non-specific disease-related disutility was derived for the BSC arm using EORTC QLQ-C30 scores from the 26-week TRIUMPH trial, although the approach included a multiplication factor of 2 to account for a 1 year duration. This approach implicitly assumed a worsening trend in quality of life which was inadequately justified in the submission. • The choice of mapping algorithm in the submission appears arbitrary given the lack of validated algorithms for PNH. The predictability of the algorithm (Longworth 2014) when used for a bleeding disorder (unrelated to cancer) is unclear. • Although there was an overall improvement in quality of life for eculizumab compared with placebo in the TRIUMPH trial from baseline to endpoint, there were fluctuations within each domain at every visit. When analysed by discrete functional scores and symptom scores, statistically significant differences were not demonstrated at every visit assessment. These fluctuations suggest changes in disease-related symptoms that may not be fully attributable to treatment. • The utility gain/loss were applied as fixed changes over the model duration. No justification was provided for this assumption, which was inconsistent with trial data from the TRIUMPH trial suggesting fluctuations in symptoms over time 	

Source: Constructed during the evaluation

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; HR, hazard ratio; PNH, paroxysmal nocturnal haemoglobinuria.

6.74 Overall, the ESC agreed that the utility values assigned to patients treated with ravulizumab lacked face validity. The calculated utility value (baseline + non-specific disease-related utility gain + reduced infusion frequency utility gain + thromboembolism disutility) for ravulizumab treated patients was 0.912 from cycle 2 onwards which exceeds matching utility values in the general population. The ESC considered that the need for a utility cap suggested the application of utility values in the model was inappropriate; noting that even with this forced cap, it is required to assume that ravulizumab treated patients who still have PNH have the same quality

of life as the general population. This assumption was inadequately justified given these patients have a life-threatening disease and may still experience lifelong disease-related symptoms. Ravulizumab is not a curative treatment and patients are likely to receive life-long treatments for disease management in addition to IV infused ravulizumab (e.g. blood transfusions).

- 6.75 The ESC also raised significant concerns regarding the methods and applicability of the calculation of the actual utility values, including the use of cancer-specific instruments (EORTC QLQ-C30) and scoring/mapping, and implausible assumptions in the discrete choice experiment (DCE) methods.
- 6.76 The submission claimed that ravulizumab is inferior in terms of safety compared to BSC but only included costs associated with meningococcal vaccine. The submission did not account for higher rates of serious infections or infusion reactions.
- 6.77 The results of the modelled economic evaluation are summarised below.

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Table 20: Results of the stepped economic evaluation for ravulizumab versus BSC

Step and component	Ravulizumab	BSC	Increment
Step 1a: Overall survival based on Kaplan-Meier curves for ravulizumab (using eculizumab as a proxy) versus BSC (using historical control as proxy) from the Kelly 2011 study, 8 year time horizon, drug and administration costs only			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY gained	7.68	6.07	1.61
Incremental cost/LY gained			\$ [REDACTED]
Step 1b: Modelled efficacy (Gompertz survival curve for ravulizumab; exponential survival curve for BSC), 8 year time horizon, drug and administration costs only			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY gained	7.69	6.30	1.39
Incremental cost/LY gained			\$ [REDACTED]
Step 2: Extrapolate to 55 year time horizon			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY gained	52.59	15.48	37.11
Incremental cost/LY gained			\$ [REDACTED]
Step 3: Incorporate age-adjusted survival cap (i.e. proportion remaining alive with PNH does not exceed general population survival estimates)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY gained	42.77	15.48	27.29
Incremental cost/LY gained			\$ [REDACTED]
Step 4: Incorporate spontaneous remission transition probability (with general population mortality within alive with remission and spontaneous remission health states)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY gained	42.77	15.48	27.29
Incremental cost/LY gained			\$ [REDACTED]
Step 5: Include anticoagulation drug costs, blood transfusion costs, specialist visit costs and meningococcal vaccine costs			
Costs	\$ [REDACTED]	\$105,255	\$ [REDACTED]
LY gained	32.61	12.01	20.60
Incremental cost/LY gained			\$ [REDACTED]
Step 6: Include baseline utilities for the alive with PNH and alive in remission health states			
Costs	\$ [REDACTED]	\$105,255	\$ [REDACTED]
QALYs	32.61	12.01	20.60
Incremental cost/QALY gained			\$ [REDACTED]
Step 7: Include disutility for thromboembolic events (event rates derived from the Kelly 2011 study)			
Costs	\$ [REDACTED]	\$105,255	\$ [REDACTED]
QALYs	32.53	11.82	20.71
Incremental cost/QALY gained			\$ [REDACTED]
Step 8: Include utility gain for reduced infusion frequency (applied to ravulizumab arm only, alive with PNH)			
Costs	\$ [REDACTED]	\$105,255	\$ [REDACTED]
QALYs	34.08	11.82	22.26
Incremental cost/QALY gained			\$ [REDACTED]
Step 9: Include non-specific disease-related utility gain (applied to ravulizumab arm) and a non-specific disease-related disutility (applied to BSC arm). Utility values were applied to the alive with PNH health state.			
Costs	\$ [REDACTED]	\$105,255	\$ [REDACTED]
QALYs	36.77	11.25	25.52
Incremental cost/QALY gained			\$ [REDACTED]
Step 10: Incorporate age-adjusted general population utility cap			
Costs	\$ [REDACTED]	\$105,255	\$ [REDACTED]
QALYs	34.71	11.25	23.45
Incremental cost/QALY gained			\$ [REDACTED]

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Step and component	Ravulizumab	BSC	Increment
Step 11: Apply 5% discount rate to costs and consequences			
Costs	\$ [REDACTED]	\$76,321	\$ [REDACTED]
QALYs	14.42	6.41	8.01
Incremental cost/QALY gained (revised base case)			\$ [REDACTED]

Source: 'Attachment 6B. Ultomiris vs BSC for PNH CUA – Excel' of the submission

Abbreviations: LY, life years; PNH, paroxysmal nocturnal haemoglobinuria; QALY, quality adjusted life years

Italicised estimates were calculated during the evaluation with the inclusion of a correction for deaths

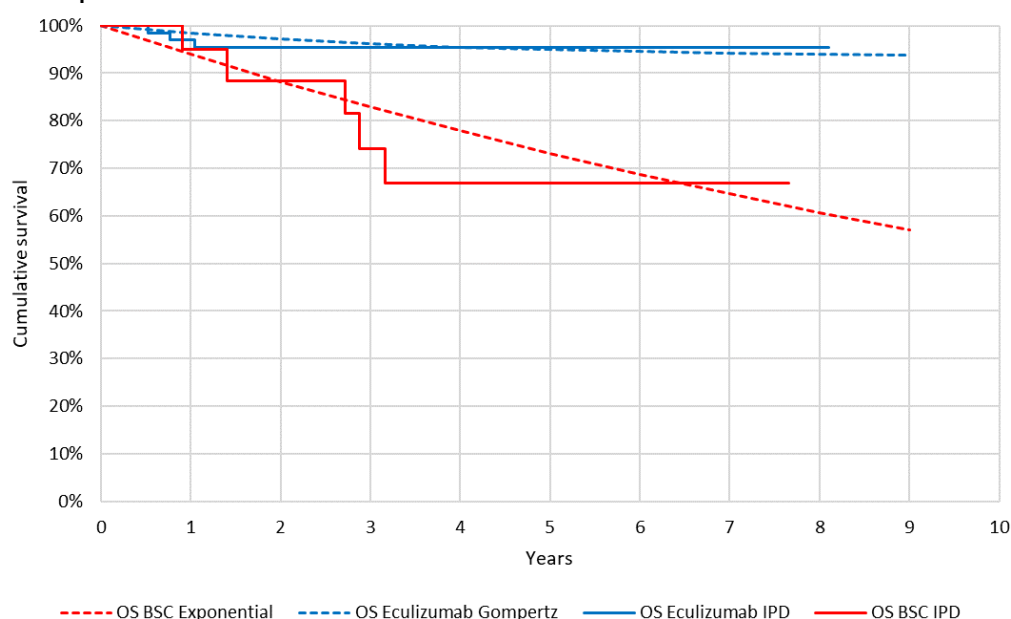
6.78 The time horizon (extrapolation to 55 years), incorporation of the spontaneous remission transition probability and discounting had the largest impacts on the stepped economic evaluation.

6.79 Based on the economic model presented in the submission, treatment with ravulizumab was associated with an incremental cost per QALY gained of more than \$200,000 compared to best supportive care for the treatment of patients with PNH.

6.80 The ESC noted there was no ravulizumab survival data and significant uncertainty remained regarding the survival data for the BSC.

6.81 During the evaluation, modelled survival curves for ravulizumab versus BSC were compared with Kaplan-Meier survival curves (reconstructed in the submission) from the Kelly 2011 publication.

Figure 3: Comparison of overall survival - reconstructed Kaplan-Meier survival curves based on the Kelly 2011 study and extrapolated curves in the economic model



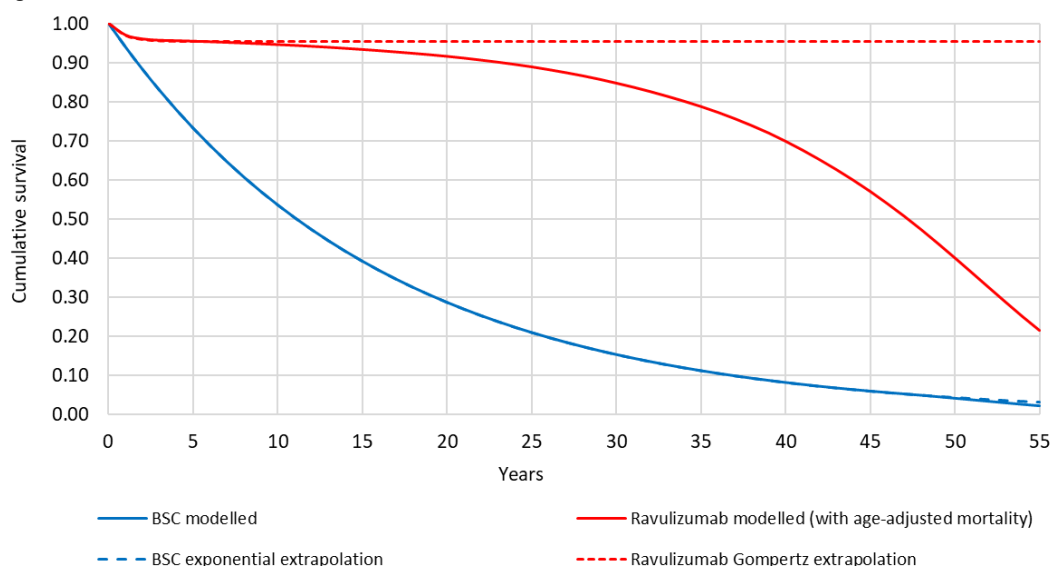
Source: Constructed during the evaluation based on 'Attachment 6B. Ultomiris vs BSC for PNH CUA – Excel' workbook of the submission
Abbreviation: OS, overall survival

6.82 Visual inspection of the curves suggest poor goodness of fit between the Kaplan-Meier survival curves and the modelled parametric curves, particularly in the first 3 years for the ravulizumab arm and for most of the data for the BSC arm. The Kaplan-Meier data

appears to be heavily affected by censoring events, which were poorly reported in the Kelly 2011 study.

6.83 During the evaluation, the following figure and table were constructed to illustrate overall survival between treatment arms and the distribution of patients in each health state (alive with PNH, alive in remission and dead) over the model duration.

Figure 4: Overall survival curves for ravulizumab and BSC in the economic model



Source: Constructed during the evaluation using 'Attachment 6B. Ultomiris vs BSC for PNH CUA – Excel' of the submission'

Table 21: Cumulative incidence over time in the model

Health state	Years												
	Baseline	5	10	15	20	25	30	35	40	45	50	55	
Alive with PNH													
Ravulizumab	100%	87.9%	79.6%	71.2%	62.6%	53.8%	44.6%	35.2%	25.8%	16.5%	8.5%	2.9%	
BSC	100%	66.2%	41.6%	23.7%	10.8%	1.6%	0%	0%	0%	0%	0%	0%	
Alive in remission													
Ravulizumab	0%	7.6%	15.0%	22.2%	29.0%	35.1%	35.1%	43.5%	44.2%	40.6%	31.7%	18.8%	
BSC	0%	7.0%	12.0%	15.5%	17.9%	19.4%	15.4%	11.3%	8.2%	6.0%	4.2%	2.3%	
Total death													
Ravulizumab	0%	4.5%	5.4%	6.7%	8.4%	11.1%	15.3%	21.2%	30.1%	42.9%	59.9%	78.4%	
BSC	0%	26.8%	46.4%	60.8%	71.3%	79.0%	84.6%	88.8%	91.8%	94.0%	95.8%	97.7%	

Source: 'Attachment 6B. Ultomiris vs BSC for PNH CUA – Excel' of the submission'

Italicised estimates were calculated during the evaluation with the inclusion of a correction for deaths

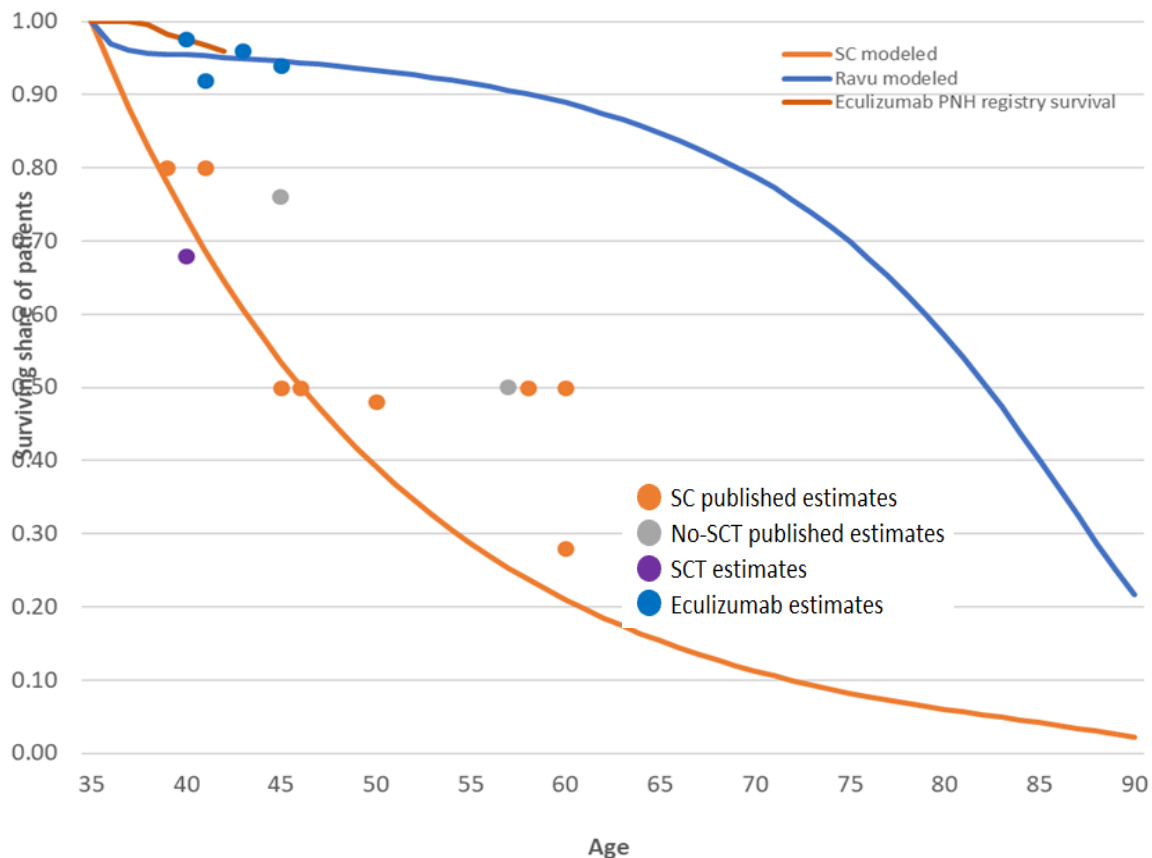
6.84 The estimates indicate a rapid separation between arms in terms of survival from the start of the model to approximately 35 years in the model, after which the curves begin to converge. Beyond 5 years in the model, patients in the ravulizumab arm can only die due to age-adjusted mortality whereas patients in the BSC arm experience an acceleration in mortality, with almost no patients remaining in the alive with PNH health state by 25 years.

6.85 The proportion of patients who transitioned to the remission state (and remain there or die of background mortality) was substantial. At 25 years in the model, almost all

surviving BSC patients were in this state and there were more surviving ravulizumab patients in this state at 35 years.

6.86 The ESC noted the submission also presented a comparison of modelled survival estimates with other estimates reported in the literature (Figure 5).

Figure 5: Overall survival modelled in the CUA, compared to published estimates



— SC modeled	— Ravu modeled	— Eculizumab PNH registry survival	● Moyo et al. (2004)
● Loschi et al. (2016) - diag. ≥ 1985	— Loschi et al. (2016) - diag. < 1985	— Socie et al. (1996)	● Hillmen et al. (1995)
● Muñoz-Linares et al. (2014)	● Socie et al. (1996)	● Nishimura et al. (2004) - USA	● Nishimura et al. (2004) - Japan
● Hillmen et al. (1995)	● de Latour et al. (2008) - no SCT	● de Latour et al. (2008) - no SCT	● de Latour et al. (2012) - only SCT
● Hillmen et al. (2013)	● Loschi et al. (2016)	● Kelly et al. (2011)	● Hill et al. (2012)

Source: Figure 62, p 244 of the submission

6.87 The submission noted that modelled survival for BSC did not fit well with published survival estimates but suggested that the base case extrapolation was representative of long term survival. The ESC considered this claim was inadequately justified. The ESC noted the published estimates suggest a wide range in survival rates. The ESC considered the BSC arm could be significantly closer to the modelled survival of eculizumab and that the most optimistic functions were selected and then adjusted for ravulizumab to fit mortality of the general population, giving the largest difference between the two.

- 6.88 The submission claimed that the survival of eculizumab-treated patients are similar to that of the general population. Published data and an ad-hoc analysis using Australian patients in the International PNH registry (source not provided, collected in 2019) suggest relatively high rates of survival in treated patients. However, the follow-up durations of these studies were relatively short given the median age of patients at diagnosis, and a lack of useful comparative data means that it is difficult to determine the magnitude of any survival benefit for eculizumab.
- 6.89 The ESC considered the magnitude of survival benefit attributed to ravulizumab (based on eculizumab as a proxy) versus BSC in the model was optimistic and implausible. The ESC considered the applicability of the Kelly 2011 retrospective study to represent contemporary BSC was unclear, and likely underestimated survival in the BSC arm.
- 6.90 The results of sensitivity analyses presented in the submission and conducted during the evaluation are summarised in following table.

Table 22: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Revised base case		8.01	\$
Correction for deaths in BSC arm (revised base case includes correction)			
Remove correction (base case in submission)	\$	7.99	\$
Baseline age (base case: 35 years)			
41 years (average of median age at diagnosis and treatment initiation from Kelly 2011)	\$	7.19	\$
46 years (median age at treatment initiation from Kelly 2011)	\$	6.37	\$
Time horizon (base case: 55 years)			
5 years	\$	1.17	\$
10 years	\$	2.55	\$
20 years	\$	4.95	\$
35 years	\$	7.13	\$
Parametric extrapolation of survival curves (base case separate models, ravulizumab: Gompertz PH, BSC: exponential AFT)			
Most favourable (exponential (AFT) both arms)	\$	7.19	\$
Least favourable (Gompertz (PH) both arms)	\$	5.03	\$
Parametric extrapolation of BSC survival curve (base case exponential AFT)			
Least favourable (log-normal (AFT))	\$	5.91	\$
Most favourable (log-logistic (AFT))	\$	8.31	\$
Parametric extrapolation of ravulizumab survival curve (base case Gompertz PH)			
Most favourable (Weibull (AFT))	\$	7.82	\$
Least favourable (log-normal (AFT))	\$	7.17	\$
Spontaneous remission transition probability (base case 0.0158)			
No spontaneous remission	\$	8.34	\$
0.0031 (Korkama 2018)	\$	8.27	\$
Non-specific disease-related utility change (base case ravulizumab: 0.101, BSC: -0.061, both applied in Year 1 and ongoing)			
No utility change in BSC arm	\$	7.61	\$
No utility change in ravulizumab arm	\$	7.31	\$
No utility change in both arms	\$	6.91	\$

Source: Table 144, p 256 and 'Attachment 6B. Ultomiris vs BSC for PNH CUA – Excel' of the submission
 Abbreviations: AFT, accelerated time failure; PH, proportional hazards

- 6.91 The submission claimed that changes to parameters had a meaningful impact on the ICER per QALY gained. However, the submission noted that in all cases, ravulizumab was not cost-effective compared with best supportive care and in some scenarios ICERs exceeded more than \$200,000 per QALY gained. The results of the sensitivity analyses indicated that the model is most sensitive to time horizon, modelled survival curves, spontaneous remission transition probability, baseline age and the non-specific disease-related utility change.
- 6.92 Changing the parametric extrapolation method for overall survival in the ravulizumab arm has minimal impact on the ICER. This is because survival is informed by general population mortality for the majority of the model duration. In the base case, for example, overall survival in the ravulizumab arm is informed by the Gompertz distribution for up to 5 years before switching to general population mortality for the remaining 50 years in the model.
- 6.93 The submission presented multivariate sensitivity analyses based on modelled overall survival using PNH mortality risk extrapolations (10, 20 and 40 years), model specification (joint, separate) and parametric distributions (exponential, Weibull, log-normal, log-logistic, Gompertz). During the evaluation, the analyses were conducted based on a revised base case including a correction for deaths in the model. The ICER was sensitive to changes in modelling parameters, ranging from around more than \$200,000 to more than \$200,000 per QALY gained.
- 6.94 During the evaluation, a number of threshold analyses were conducted to determine the price reduction required for ravulizumab to be more cost-effective. In order to achieve high cost-effectiveness thresholds of \$100,000, \$200,000 and \$300,000 per QALY gained the corresponding price reductions required would be █%, █% and █%. The ESC noted that ICERs of around this magnitude have previously been considered by PBAC for other rare conditions. The ESC also acknowledged these required price reductions are based on the economic model presented in the submission, which was considered highly uncertain.
- 6.95 The ESC noted that in the event eculizumab for PNH was made available on the PBS, a cost-minimisation analysis of ravulizumab versus eculizumab would be appropriate, given ravulizumab appears to have no clinically meaningful advantage compared to eculizumab.

Drug cost/patient/year

- 6.96 The estimated drug cost for ravulizumab per patient per year was \$ █ in the first year (including loading dose and additional maintenance dose, based on the proposed AEMP of \$ █ per vial and an average of █ vials using trial-based weight distribution).
- 6.97 The estimated drug cost for ravulizumab per patient per year, was \$ █ in subsequent years based on the proposed AEMP of \$ █ per vial and 69.6 vials per year (calculated using trial-based weight distribution and 8-weekly dosing interval).

in a calendar year). There was a difference in costs estimated using an average over 10 years (accounting for differences in total doses in odd and even years) used in the comparison of ravulizumab versus BSC, calculated as \$ [REDACTED] in subsequent years (based on the proposed AEMP of \$ [REDACTED] per vial and an average of [REDACTED] vials using trial-based weight distribution).

- 6.98 The estimated drug cost for eculizumab per patient per year, during maintenance years was \$ [REDACTED] based on an AEMP of \$ [REDACTED] per vial and [REDACTED] vials per year (calculated using fixed maintenance dose and 2-weekly dosing interval).
- 6.99 The average eculizumab cost per patient to the LSDP for the period 1 April 2019 to 31 March 2020 was \$ [REDACTED] (incl GST). This cost incorporates both the additional costs for loading doses for new patients and the reduction in costs associated with new patients commencing part way through the year.

Estimated PBS usage & financial implications

- 6.100 This submission was not considered by DUSC. The submission used a mixed market share/epidemiological approach to estimate the utilisation and financial impact for ravulizumab using three sets of patients (key inputs summarised in the table below):
- Incident PNH patients who meet eligibility criteria and were previously untreated with eculizumab (treatment-naïve), based on an agreed growth in the Deed of Agreement for eculizumab on the LSDP;
 - Prevalent PNH patients who are currently or previously treated with eculizumab (treatment-experienced) based on epidemiological data; and
 - Grandfathered ravulizumab patients.

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Table 23: Key inputs for eligible population estimates

Parameter	Value applied and source	Comment
Treatment-naïve patients		
Incident patients previously untreated	█ patients per year based on agreed growth in the current Deed of Agreement for eculizumab on the LSDP	Data informing the fixed growth were not provided in the submission. The numbers appeared inconsistent with the difference in patient estimates in the current Deed of Agreement provided in the submission
Complement inhibitor uptake	100%, assumed.	No data were provided to support this assumption.
Ravulizumab uptake	93%, based on sponsor-commissioned patient preference study in patients treated with eculizumab (Trial 302)	Preferences elicited from a treatment-experienced population are unlikely to represent preferences in a treatment-naïve population. Uptake rates in a treatment-naïve population may be higher.
Ravulizumab persistence	90% in the initial year, then 100% in continuing patients, assumed	No data were provided to support this assumption.
Treatment-experienced patients		
Adult Australian population	20,100,838 in Year 1 increasing to 21,744,502 in Year 6. Australian Bureau of Statistics Population Projection (2020-2025)– 3222.0 Series B, adults 18-100 years inclusive.	The submission inappropriately used 2020-2025 population estimates as inputs for 2021-2026 estimates without any adjustment.
Prevalence	0.0016%, based on Hill 2006 epidemiological study in Yorkshire, England in patients diagnosed with PNH between 1991 and 2006.	Overall, the prevalence of PNH is likely to be an underestimate as it is based on diagnosed patients only. The data were captured over a 15-year period and likely to be higher over longer time frames.
Proportion of eligible patients	43%, based on proportion with clone size greater than 10% in Hill 2006 study.	It was unclear if the clone size distribution reported was at diagnosis only due to limited detail in the abstract. Eligibility was based on clone size only; and did not account for other biochemical measures (e.g. LDH levels, blood counts) and clinical symptoms that were part of the requested restriction.
Complement inhibitor uptake	100%, assumed.	No data were provided to support this assumption.
Previously treated patients who are restarting treatment	Less than 10,000 per patient per year, assumed based on sponsor's experience with eculizumab on the LSDP	No data were provided to support this assumption.
Proportion of treated patients switching to and initiating ravulizumab	█% in Year 1, decreasing to █% in Year 6. The approach in the submission assumes the majority of switching from eculizumab to ravulizumab occurs within 2-3 years and subsequently, new ravulizumab use was driven by restarting patients.	No data were provided to support this assumption
Ravulizumab persistence	90% in the initial year, then 100% in continuing patients, assumed	No data were provided to support this assumption.
Grandfathered patients		
Grandfathered ravulizumab patients	Less than 10,000 Australian patients currently receiving ravulizumab through sponsor's trials (Study 103, dose-escalation trial; Trials 301 and 302). The submission requested grandfathering provision for these patients.	The submission did not provide an assessment of patient eligibility based on the requested restriction for ravulizumab. The submission only accounted for maintenance costs in Year 1, after which there were no further costs attributed to this population.

Source: Section 4, p 259-279 and 'Attachment 7. Ultomiris Utilisation and Cost Model – Excel' workbook of the submission
Italicised estimates were used during the evaluation to simplify the overly complex approach used in the submission

6.101 The total market size for complement inhibitors was estimated using an overly complex, multi-step derivation of a treatment-naïve population (market share

approach) and treatment-experienced population (epidemiological approach) with the addition of grandfathered patients. There is likely to be considerable overlap between these populations, which cannot be reliably estimated using mutually exclusive approaches. The reliability of combined patient estimates in this model was uncertain. It may be more appropriate to use a single, market share approach given available estimates of eculizumab use on the LSDP.

6.102 There were multiple key assumptions used that were inadequately supported in the submission:

- Agreed growth numbers (■ per year) could not be reconciled with year-to-year differences in patient estimates of between less than 10,000 to less than 10,000 patients based on the current Deed of Agreement;
- The number of eligible patients in the treatment-experienced population was based on a prevalence of diagnosed patients only and the proportion reported having a clone size greater than 10% (which can fluctuate over time). The submission did not account for other criteria in the requested restriction;
- The submission assumed 100% of eligible patients would be treated with a complement inhibitor. In practice, it is likely that there is a prevalent pool of patients who would not receive treatment due to patient- and physician-related factors (e.g. safety concerns, co-morbidities, treatment burden);
- The submission assumed no market growth due to the availability of ravulizumab. This assumption was inadequately justified given the clinical claim of non-inferior (potentially superior) efficacy and reduced treatment burden associated with ravulizumab compared with eculizumab;
- No data were presented in support of persistence estimates, the assumed less than 10,000 patients per year who previously ceased treatment and were restarting therapy, and the assumed proportions of patients switching from eculizumab to ravulizumab.

6.103 There was a significant number of patients discontinuing treatment in the first year (90% persistence rate) who were not adequately accounted for and could not be reconciled with prevalence and incidence estimates.

6.104 It was unclear if there was any overlap between the grandfathered ravulizumab patients and the prevalent pool informing the treatment-experienced population. There was no assessment of these patients against eligibility criteria in the requested PBS restriction.

6.105 The table below presents the estimated use and financial impact of ravulizumab listing on the PBS.

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Table 24: Estimated use and financial impact of ravulizumab to the PBS

	Year 1 (2021)	Year 2 (2022)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Year 6 (2026)
Estimated use of ravulizumab						
Ravulizumab initial patients						
- Treatment naïve						
- Treatment experienced						
Ravulizumab continuing patients						
- Treatment naïve						
- Treatment experienced						
- Grandfathered						
Total initial year scripts (vials per patient)						
Total subsequent year scripts (vials per patient)						
Total scripts						
Net cost of ravulizumab to the PBS (weighted DPMQ \$ per script)	\$	\$	\$	\$	\$	\$
Initial scripts from treatment-experienced patients switching to ravulizumab (8.7 vials loading dose only) ^a			-1			
Cost offset (weighted DPMQ \$)	-\$	-\$	-\$	-\$	-\$	-\$
Net cost of ravulizumab to PBS including RSA rebate for loading dose	\$	\$	\$	\$	\$	\$
Cost offsets due to substitution of eculizumab use on the LSDP						
Substituted initial patients						
Substituted continuing patients						
Grandfathered ravulizumab patients (continuing)						
Initial year scripts (vials/patient)						
Subsequent year scripts (vials/patient)						
Total scripts						
Cost offset due to substitution (\$ per vial) ^b	-\$	-\$	-\$	-\$	-\$	-\$
Cost of treatment administration						
Total ravulizumab patients						
MBS costs for ravulizumab infusions (\$646.75/year) ^c	\$	\$	\$	\$	\$	\$
MBS costs offset for eculizumab infusions (\$1,718.60/year) ^c	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to Government due to ravulizumab listing						
Net cost of ravulizumab including all cost offsets	\$	\$	\$	\$	\$	\$

Source: Section 4, 259-279 and 'Attachment 7. Ultomiris Utilisation and Cost Model - Excel' workbook of the submission

^a The sponsor proposed a risk sharing arrangement to provide

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^b AEMP per vial of eculizumab including 10% statutory price reduction in 2021

^c Based on annual number of infusions during maintenance phase only for ravulizumab (6.5) and eculizumab (26)

Note: The weighted DPMQ for ravulizumab was estimated based on 90% public hospital and 10% private hospital use

There was an error in the budget impact model in the submission. The submission counted the loading doses for eculizumab twice in treatment-experienced patients switching to ravulizumab (i.e. ■ vials instead of ■ vials). These estimates were corrected during the evaluation.

The redacted table shows that at Year 6, the estimated number of patients was less than 500 and the net cost to the PBS would be less than \$10 million.

- 6.106 Overall, both the estimated total number of patients who will be eligible for treatment with ravulizumab or eculizumab via the LSDP and the expected annual increase in patients (see also Table 26) are higher than currently (current LSDP patients = ■, new patients: ■ in 2018; ■ in 2019; and ■ in 2020), even taking into account the number of patients currently receiving alternative treatments in clinical trials (n = ■). [Communication LSDP, 6 May 2020].
- 6.107 The net cost of ravulizumab to the PBS for patients with paroxysmal nocturnal haemoglobinuria was \$30 - \$60 million in Year 1, increasing to \$60 - \$100 million in Year 6, a total of more than \$100 million over 6 years. The net cost including a cost offset due to a proposed risk sharing agreement (■) was \$30 - \$60 million in Year 1, increasing to \$60 - \$100 million in Year 6, a total of more than \$100 million over 6 years.
- 6.108 The net cost of ravulizumab to the Government including cost offsets due to substitution of eculizumab (LSDP drug acquisition and treatment administration costs) was less than \$10 million in Year 1, increasing to less than \$10 million in Year 6, a total of \$30 - \$60 million over 6 years.
- 6.109 The submission claimed the increased cost to Government was due to the price differential between the requested price for ravulizumab which was based on the current price of eculizumab, and the expected price of eculizumab used in the model which includes a 10% price reduction from April 2021. Although the price differential for eculizumab accounted for the majority of increased costs, there was still an increase in cost to Government when using the current price of eculizumab (less than \$10 million over 6 years, calculated as a sensitivity analysis during the evaluation).
- 6.110 The requested price of ravulizumab was based on the economic analysis of ravulizumab versus eculizumab, but priced using dosing regimens in the maintenance phase only. The drug cost for ravulizumab is higher compared to eculizumab during the initiation year, which contributes to the increased cost to Government. There were also additional costs associated with dispensing fees and mark-ups for ravulizumab supplied in private hospitals. However, the impact on financial estimates was minimal given relatively low use (10%) assumed in the submission.
- 6.111 The estimated net cost of ravulizumab is highly uncertain due to the following reasons:

- Costs associated with grandfathered ravulizumab patients were only attributed in Year 1 of the model. This was inappropriate and would substantially underestimate ravulizumab costs in subsequent years;
- Grandfathered ravulizumab patients were inappropriately included as part of cost offsets due to substitution of eculizumab;
- The submission inappropriately assumed that each vial of ravulizumab would represent one prescription. While there is no impact to estimated costs for treatments on the LSDP, this approach was inconsistent with the requested restriction for ravulizumab on the PBS (number of vials per script would be requested by the treating physician);
- The submission did not include estimates for patient co-payments, which would result in reduced costs to Government;
- Cost offsets due to substitution of eculizumab were inappropriately calculated based on the distribution of initial and continuing ravulizumab patients. Cost offsets should be calculated based on continuing patient costs only which are lower than initial year costs; and
- Cost offsets due to reduced infusion frequency with ravulizumab were overestimated as infusion costs were based on the maintenance phase only and did not account for a higher infusion frequency during the initial year of ravulizumab.

Quality Use of Medicines

6.112 The submission detailed the implementation of risk minimisation measures, including targeted education materials, controlled distribution in Australia, and annual meningococcal vaccination reminder, to be managed via a digital risk minimisation platform. The sponsor will require a completed certificate of vaccination against N. meningitides and/or treatment with prophylactic antibiotics to allow distribution to occur. The sponsor also indicated the potential use of existing Patient Support Programs that are in place for eculizumab.

Financial Management – Risk Sharing Arrangements

6.113 The submission proposed a risk sharing arrangement to manage uncertainty in costs to Government should ravulizumab be listed on the PBS. The proposal is based on two linked components; [REDACTED] and a [REDACTED] [REDACTED] in patients previously treated with eculizumab.

6.114 The submission noted that eculizumab is available on the LSDP [REDACTED] [REDACTED] between the Government and the sponsor. The proposal in the submission was based on the assumption that ravulizumab could [REDACTED] [REDACTED].

6.115 The submission stated that the requested price of ravulizumab is [REDACTED] [REDACTED]. The sponsor acknowledges that the price of eculizumab will decrease in April 2021 by [REDACTED] % ([REDACTED]) while the

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requested price of ravulizumab will remain unchanged. The sponsor proposed a risk share agreement to ensure Government expenditure per patient on ravulizumab

6.116 The submission proposed a [redacted] without the listing of ravulizumab over 6 financial years.

Table 25: Proposed Commonwealth Payment Thresholds for [redacted] based on estimated use of eculizumab without listing of ravulizumab over 6 financial years (based on calendar year estimates)

	Year 1 (2021-22)	Year 2 (2022-23)	Year 3 (2023-24)	Year 4 (2024-25)	Year 5 (2025-26)	Year 6 (2026-27)
Total patients treated with eculizumab (world without ravulizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Patients otherwise treated with ravulizumab (from budget impact model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Treatment naïve (complement of ravulizumab estimates)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Treatment experienced (complement of ravulizumab estimates)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial year patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing year patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total initial year scripts ([redacted] vials/patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total continuing year scripts ([redacted] vials/patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total eculizumab scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost to the LSDP (\$ [redacted] per script)^a [Proposed Commonwealth Payment Threshold]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Source: Table 170, p 283 and 'Total PNH calculation' spreadsheet of 'Attachment 7. Ultomiris Utilisation and Cost Model – Excel' workbook of the submission'

^a Estimated price based on AEMP \$ [redacted] x [redacted] (incorporating 10% statutory price reduction from April 2021)

The redacted table shows that at Year 6, the estimated number of patients was less than 500 and the net cost to the PBS would be between \$60 - \$100 million.

6.117 The submission stated that the thresholds in the table above would apply to both eculizumab and ravulizumab and the sponsor would provide a [redacted]. The submission noted that this proposal was based on calendar years and may require amendment to correspond to the time of listing.

6.118 The approach used to estimate the use of eculizumab without listing of ravulizumab was poorly documented. The estimated use of eculizumab appeared to be based on ravulizumab estimates from the budget impact model, and a calculated complement number for the treatment-naïve population and treatment-experienced populations. This approach incorporates all uncertainties with estimates that were derived using a complex, poorly justified approach and the use of inadequately justified key

assumptions surrounding: market growth, prevalence and treated estimates, and circumstances of use. This resulted in both the estimated patient numbers and proposed payment thresholds being higher than justified by current LSDP expenditure, even taking into account patients currently receiving treatment through clinical trials.

- 6.119 There were additional concerns with these estimates due to a significant number of ravulizumab patients discontinuing treatment in the first year (90% persistence rate) who were not adequately accounted for; the assumption that patients who restart treatment (included in ravulizumab estimates) are attributed the cost of continuing patients; and the inclusion of grandfathered ravulizumab patients in Year 1 eculizumab estimates. Overall, the proposed payment thresholds should not be considered reliable.
- 6.120 The submission claimed that a [REDACTED] can be inferred through the proposed [REDACTED], based on the assumed split between eculizumab patients incurring initial year versus maintenance year costs (i.e. only agreed growth patients incur initial year costs). Consequently, the submission claimed that the use of these [REDACTED] suggests no additional expense to Government due to the loading dose of ravulizumab in patients switching from eculizumab.
- 6.121 Alternatively, if the preference for Government is for [REDACTED], then the sponsor is willing to monitor the loading dose at [REDACTED]
[REDACTED]
[REDACTED] | [REDACTED] | [REDACTED]
- 6.122 Loading dose cost offsets for ravulizumab were based on [REDACTED] [REDACTED] vials), and does not fully account for the increased cost due to a higher number of vials administered during the initial year (estimated average of [REDACTED] vials based on trial-based weight distributions).
- 6.123 The table below presents the net cost to Government of ravulizumab listing on the PBS with the application of the risk share agreement.

Table 26: Net cost to Government of ravulizumab listing on the PBS (with RSA)

	Year 1 (2021-22)	Year 2 (2022-23)	Year 3 (2023-24)	Year 4 (2024-25)	Year 5 (2025-26)	Year 6 (2026-27)
Net cost of ravulizumab to the PBS with loading dose RSA rebate (weighted DPMQ \$██████████)	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████
Cost of eculizumab on the LSDP (\$██████████ per vial)	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████
Cost of ravulizumab and eculizumab to the Government	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████
Proposed Commonwealth Payment Threshold	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████
Estimated rebate from sponsor	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████

Source: Table 166, p 279 of the submission

6.124 The submission claimed the increasing net cost of ravulizumab and eculizumab over time was due to the 10% price reduction of eculizumab from 2021. Although the price differential was the primary driver of increased costs, there were also additional costs due to higher initial year costs for ravulizumab compared with eculizumab.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend ravulizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH). The PBAC considered the clinical evidence presented in the submission demonstrated that ravulizumab is likely to be non-inferior compared to eculizumab in the short-term. However, the PBAC considered that due to the lack of long-term follow-up data available, it was uncertain whether a patient’s lifespan would be substantially extended as a direct consequence of the use of ravulizumab. The PBAC also considered the applicant’s economic model did not provide a valid means of estimating the cost-effectiveness of ravulizumab for PBS listing and was therefore not informative for decision-making.

7.2 The PBAC considered eculizumab, which is subsidised through the Life Saving Drugs Program (LSDP), was the appropriate primary comparator. The PBAC noted BSC was included as a secondary comparator as there is currently no PBS-listed medicine available specifically for the treatment of patients with PNH. The PBAC considered this was an appropriate way to determine the cost-effectiveness of a PBS listing for ravulizumab, however it was noted all data comparing ravulizumab to BSC was indirect, via a comparison of eculizumab against BSC, or from using eculizumab vs BSC as a proxy.

7.3 The PBAC noted the submission was based on two short head-to-head randomised non-inferiority trials comparing ravulizumab to eculizumab over 26 weeks, Trial 301 (treatment-naïve patients) and Trial 302 (previously stable on treatment with eculizumab). The PBAC also noted all comparative effectiveness outcomes were

within the bounds of the pre-specified non-inferiority margins from the trials, and the results indicated non-inferiority of ravulizumab to eculizumab for all measured outcomes, including transfusion avoidance; haemolysis (measured by LDH change); breakthrough haemolysis (BTH); quality of life; and stabilised haemoglobin (see Comparative effectiveness section).

- 7.4 The PBAC noted the submission's claim of non-inferior survival of ravulizumab compared to eculizumab, and superior survival compared to BSC, was entirely based on the available survival data for eculizumab, and an assumption that non-inferiority for measured surrogate outcomes (Tables 5-8) may be extended to survival, and that ravulizumab is a modified eculizumab molecule. The PBAC also noted eculizumab's survival data presented in the submission varied significantly in relation to duration of follow-up (refer to Table 14) and that the submission used survival data from a retrospective study of eculizumab versus a matched historical control (Kelly 2011) as a proxy for ravulizumab to inform the economic model against BSC. The PBAC noted the draft report of the LSDP Review of eculizumab stated that 'published medical literature demonstrates survival in PNH patients treated with eculizumab is higher than that of untreated patients', whilst also noting that studies had a significant risk of bias. The PBAC agreed with the ESC (see paragraph 6.46) that it may not be reasonable to assume that the superior survival benefit previously accepted for eculizumab compared to BSC can be applied to ravulizumab compared to best supportive care, in the absence of any long term survival data for ravulizumab. Moreover, the magnitude of any survival benefit of eculizumab compared to BSC is itself unclear, given the lack of contemporary data for BSC survival outcomes.
- 7.5 The PBAC noted the submission's claim that based on results of the meta-analysed data from the key trials, ravulizumab is superior in terms of reduction in risk of BTH compared to eculizumab. However, the PBAC agreed with the ESC and considered that ravulizumab was non-inferior to eculizumab in regards to BTH (see paragraphs 6.43 & 6.44).
- 7.6 The PBAC noted the Sponsor Hearing and Consumer Comments, recognising the strong sentiments expressed around the preference for ravulizumab's reduced infusion frequency compared to eculizumab. However, the Committee considered any QoL improvement potentially offered by swapping to the eight-weekly dosing regimen was not captured by the QoL measures used in the clinical trials and therefore the submission's claim of improved QoL was not adequately supported.
- 7.7 The PBAC did not accept the sponsor's assertion in the pre-PBAC response, that "Patients in the trial were still required to have the same number of clinic visits and ongoing fortnightly monitoring regardless of which arm they were randomised to, hence patients in the ravulizumab arm did not experience the benefit of 8 weekly infusions. It is therefore not surprising that QoL results did not reach significance in the trial." If ravulizumab does lead to a significant improvement in QoL versus eculizumab, PBAC would have expected to see this reflected in a significant improvement reported in FACIT-fatigue scores (Table 8) for patients on ravulizumab

versus eculizumab. However, this was not observed. PBAC also questioned the appropriateness of the EORTC QLQ-C30 scores reported in the trials, noting the EORTC QLQ-C30 is specifically used to assess the health-related QoL of cancer patients.

- 7.8 Overall, the PBAC considered the submission's claim of non-inferior effectiveness compared to eculizumab was reasonable in the short-term. However, PBAC considered that due to the lack of long-term follow-up data available for ravulizumab, it was uncertain whether a patient's lifespan would be substantially extended as a direct consequence of the use of ravulizumab.
- 7.9 The PBAC considered the submission's claim of non-inferior safety compared to eculizumab and inferior safety compared to BSC was appropriate.
- 7.10 The PBAC noted the submission presented a cost-utility analysis of ravulizumab versus BSC to establish the cost-effectiveness of ravulizumab for listing on the PBS. However, the PBAC agreed with the ESC and considered there was substantial uncertainty in the modelled economic analyses, and considered the model structure used in the comparison versus BSC lacked face validity and was therefore not reliable for PBAC decision making.
- 7.11 The PBAC noted that during the evaluation, modelled survival curves for ravulizumab versus BSC were compared with Kaplan-Meier survival curves (reconstructed in the submission) from the Kelly 2011 publication. The PBAC agreed with the ESC that the magnitude of survival benefit attributed to ravulizumab (based on eculizumab as a proxy) versus BSC in the model was optimistic and implausible, with most of the outcomes accrued in the extrapolated period. The applicability of the Kelly 2011 retrospective study to represent contemporary BSC was unclear, and likely underestimated survival in the BSC arm (see paragraph 6.87).
- 7.12 The PBAC agreed with the ESC that the utility values assigned to patients treated with ravulizumab lacked face validity, considering the need for a utility cap in the ravulizumab arm suggested the application of utility values in the model was inappropriate (see paragraph 6.72).
- 7.13 The PBAC noted that based on the economic model presented in the submission, treatment with ravulizumab was associated with an incremental cost per QALY gained of more than \$200,000 compared to BSC for the treatment of patients with PNH. The PBAC further noted the ICER was most sensitive to the time horizon, modelled survival curves, spontaneous remission probability, the baseline age of 35 years and non-specific disease related utility change (Table 22). However, given the PBAC considered the model lacked face validity and was unreliable for decision making, it also considered the ICER of more than \$200,000 per QALY gained was inaccurate and did not reflect the true cost-effectiveness of ravulizumab versus BSC.
- 7.14 The PBAC considered that based on the threshold analyses conducted during the evaluation, a price reduction would be required in order for ravulizumab to be considered cost-effective, however the magnitude of the reduction remained

uncertain given the analyses were based on the economic model provided in the submission, which was considered unreliable (paragraph 6.92). The PBAC recalled that it has accepted higher cost-effectiveness thresholds for other rare conditions in recent years, whereas this was not the case at the time of eculizumab consideration in 2010.

- 7.15 The PBAC considered the net cost of treatment with ravulizumab was highly uncertain and should be re-examined in any resubmission (see paragraph 6.109).
- 7.16 The PBAC noted the submission proposed a risk share arrangement to manage uncertainty in cost to Government should ravulizumab be listed on the PBS, with the proposal based on the assumption ravulizumab could be [REDACTED]. The PBAC considered the estimated patient numbers and proposed payment thresholds were over-estimated and higher than justified by current LSDP expenditure, even taking into account patients currently receiving treatment through clinical trials.
- 7.17 The PBAC considered any resubmission should be a major resubmission and require a new economic model and, potentially, a significant price reduction.
- 7.18 Further, the PBAC noted that eculizumab is currently subject to a post-market review by the LSDP Panel and the recommendation to the Chief Medical Officer at the end of that review may include advice on the possibility of re-considering eculizumab for the PBS. As such the ravulizumab consideration for PBS listing would be impacted by this outcome.
- 7.19 The PBAC considered the outcome for this submission should be formally communicated to the LSDP Panel, noting the LSDP's mandate to provide advice on future funding arrangements of currently listed drugs, including referral back to the PBAC for further consideration for PBS listing.
- 7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Alexion welcomes the PBAC's acknowledgement that ravulizumab is non-inferior to eculizumab, however is disappointed with the PBAC decision to reject. We are committed to working with the PBAC and the Department of Health to pursue access for adult patients with PNH who are calling for this new 8-weekly treatment option, which will reduce the burden of fortnightly infusions.