Cost-effectiveness evaluation of ravulizumab (Ultomiris) by the academic group

[Version 1.2]

[Version 1, December 25, 2020]

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[Table of abbreviations]

Abbreviation	Formal description
ACT	Appropriate Comparator Therapy
AE	Adverse Event
AUD	Australian Dollar
BSC	Best Supportive Care
BTH	Breakthrough Hemolysis
C5	Complement component 5
CAC	Complement Amplifying Condition
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
DCE	Discrete Choice Experiment
DPC	Diagnosis Procedure Combination
EBM	Evidence-Based Medicine
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life-Questionnaire-Core-30
EQ-5D	EuroQol 5 Dimension
FACIT	Functional Assessment of Chronic Illness Therapy
HAS	Haute Autorité de Santé
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LDH	Lactate Dehydrogenase
MAVE	Major Adverse Vascular Events
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PNH	Paroxysmal Nocturnal Hemoglobinuria
pRBC	packed Red Blood Cell
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-Adjusted Life Year
QOL	Quality of Life

RCT	Randomized Controlled Trial
RQ	Research Question
SMC	Scottish Medicines Agency
SR	Systematic Review
ULN	Upper Limit of Normal

0. Analytical framework

The evaluated product is ravulizumab (Ultomiris) and the manufacturer is Alexion Pharma G.K. Ravulizumab is a therapeutic agent for paroxysmal nocturnal hemoglobinuria (PNH) and was selected as a target product of the cost-effectiveness evaluation at Central Social Insurance Medical Council (CSIMC) on August 28, 2019. The market size of ravulizumab is JPY 33.1 billion and the category of the cost-effectiveness evaluation is H1 (The market size is 10 billion yen or more). The analytical framework of ravulizumab was established as shown in Table 0-1 after the Expert Committee of Cost-Effectiveness evaluation on December 12, 2019.

Table 0-1 Analytical framework

Population	Paroxysmal nocturnal hemoglobinuria
Comparator	Eculizumab (Soliris)
Reason for selection of comparator	In Japan, eculizumab is the only drug indicated for paroxysmal nocturnal hemoglobinuria, the indication of ravulizumab. Therefore, eculizumab is considered appropriate, being “a technology likely to be a substitute for the technology analyzed as of the time when the technology analyzed is introduced to treat the target population of analysis, which has a higher therapeutic effect and is used widely in medical practice.”
Other perspective in addition to public healthcare payer	Yes (Details:) No
Outcome and the reason if QALY is not used.	Not applicable (QALY is used CEA)
Other	The following sensitivity analysis (scenario analysis) is performed. Analysis compared to best supportive care (BSC) A conventional therapy (BSC) except for eculizumab can be the comparator technology for “patients who have an indication for eculizumab therapy but remain untreated.” However, because the number of relevant patients was expected to be limited and there might be uncertainty in the analysis, it was considered to perform the analysis not by base case analysis but by sensitivity analysis

	(scenario analysis).

1. Summary of other HTA agency reviews

1.1 Summary

The manufacturer reported results of the evaluations of ravulizumab by HTA agencies in other countries. Accordingly, the evaluation results by these agencies were investigated and compared with manufacturer's submission. A summary of the evaluations in these countries is provided in Table 1-1. In the next step, the cost-effectiveness evaluations of ravulizumab by HTA agencies in these countries were reviewed in detail. A cost-effectiveness evaluation of ravulizumab was performed only in Australia (Table 1-2).

Table 1-1 Evaluation Status

Country	Organization	Evaluation results	
		Manufacturer	Academic group
UK	NICE	Evaluation ongoing	Evaluation ongoing [Final scope was published in July 2020.][1]
	SMC	None	None
France	HAS	None	None
Germany	IQWiG	No description in manufacturer's submission	RQ1: Adult patients with paroxysmal nocturnal hemoglobinuria (PNH) with hemolysis with clinical symptoms indicative of high disease activity ACT: eculizumab **<No additional benefit>** RQ2: Adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months ACT: eculizumab

			<No additional benefit> [November 2019, February 2020][2, 3]
Canada	CADTH	None	None
Australia	PBAC	None	**Not recommended (rejected)**[4] [November 2020]

*The submission date of the report of the manufacturer was May 2020.

Table 1-2 Details of cost-effectiveness analysis in Australia (PBAC)

Country	Australia
Organization	PBAC[4]
URL	https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2020-07/batch_2/ravulizumab-solution-concentrate-for-iv-infusion-300-mg
Target technology	Ravulizumab
Evaluation results	Not recommended
Details of the condition	Not applicable
Target disease	PNH
Comparator	(1) Eculizumab (primary comparator) (2) BSC (secondary comparator)
ICER	(1) Not disclosed (2) ≥AUD200,000/QALY

1.2 Review results

As a results of review by the academic group, the manufacturer's report did not include the evaluation status in Germany [5]. This was investigated, and it was found that evaluation results of ravulizumab had been published in November 2019 and February 2020 and ravulizumab had been reported to show “no additional benefit”[2, 3]. In addition, although the evaluation result in Australia was stated as “none” in the report of the manufacturer, it was found that evaluation results had been published in November 2020 later than the submission of the report of the manufacturer (May 2020), showing that ravulizumab was “not recommended”[4].

1.3 Issues raised in HTA agencies

Considering the issues raised in the assessment process by HTA organizations, the issues that may be helpful for this evaluation was summarized as follows.

<NICE>[1]

- While the evaluation of ravulizumab has been ongoing at NICE, the final scope includes the following outcome measures that should be considered to be included in evaluation: overall survival, hemolysis (measured by LDH level), breakthrough hemolysis, transfusion avoidance, stabilized hemoglobin, thrombotic events, adverse reactions to treatment, and health-related QOL (HRQOL) (patients and carers).

<IQWiG>[2, 3]

- Additional benefit of ravulizumab versus eculizumab was examined by IQWiG for the following two target populations.
  - RQ1: Adult patients with paroxysmal nocturnal hemoglobinuria (PNH) with hemolysis with clinical symptom(s) indicative of high disease activity
  - RQ2: Adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months
- RQ1 and RQ2 were evaluated on the basis of 301 study and 302 study, respectively, using the following outcome measures: all-cause mortality, MAVEs, fatigue (FACIT-Fatigue), transfusion avoidance, HRQOL, serious AEs, discontinuation due to AEs, and meningococcal infection.
- From the evaluation, it was concluded that neither RQ1 nor RQ2 indicated any additional benefit of ravulizumab versus eculizumab.
- Subsequently, in February 2020, a report of supplementary evaluation using BTH as an outcome measure was published. In this evaluation, BTH is defined as "at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin <10 g/dL], major adverse vascular event [MAVE], dysphagia, erectile dysfunction)" and, at the same time, "patients must have Lactate dehydrogenase (LDH) must be elevated to at least twice the ULN after LDH has fallen below 1.5 x upper limit of normal (ULN) at

the time of treatment". After review, BTH was not used to evaluate ravulizumab for the following reasons.

- The symptoms used to define BTH (fatigue, abdominal pain, dyspnea, dysphagia, and erectile dysfunction) include subjective factors in patients.
- Clinical studies did not assure the complete recording of the aforementioned symptoms.
- 301 and 302 are open-label studies with high risk of bias.

<PBAC>[4]

- The manufacturer evaluated additional benefit and cost-effectiveness of ravulizumab versus eculizumab (primary comparator) and BSC (secondary comparator) in adult patients with PNH.
- The following outcome measures were used for the evaluation of additional benefit: for comparison with eculizumab, transfusion avoidance, the presence or absence of hemolysis, occurrence of BTH, QOL, and stabilization of hemoglobin; for comparison with BSC, transfusion avoidance, QOL, and the presence or absence of hemolysis.
- The manufacturer reported the noninferiority of ravulizumab to eculizumab in terms of efficacy and safety. The manufacturer asserted that ravulizumab was superior to eculizumab in terms of occurrence of BTH based on the results of meta-analysis of 301 and 302.
- However, PBAC determined that no additional benefit of ravulizumab on BTH had been demonstrated because of the following reasons.
  - 301 study was a noninferiority study with the primary endpoints of transfusion avoidance and normalization of LDH levels, and 302 study was a noninferiority study with the primary endpoint of percent change in LDH; in the individual studies alone, the power to detect statistically significant differences in BTH might have been insufficient. Meanwhile, whereas 301 involved patients naive to complement inhibitor therapy, 302 involved patients previously treated with complement inhibitor therapy; considering the difference in target population, pooled analysis by meta-analysis might be inappropriate.
  - In 301 and 302, eculizumab therapy was performed every 14 days, and the adjustment of dosing schedule within the 2-day timeframe (or adjustment by a dose increase), which is considered as needed, was not performed for the management of BTH. For this reason, there is uncertainty about bringing the

results of these clinical studies into general use in patient populations in actual clinical settings.

- BTH, which is characterized by increased LDH levels, cannot be said to be clinically significant unless associated with other clinical characteristics such as fatigue and the need of transfusion.

- The manufacturer reported that ravulizumab is superior to BSC in terms of efficacy and inferior to BSC in terms of safety.
- However, because the comparison of ravulizumab with BSC was based on indirect comparison using eculizumab as the anchor, PBAC pointed out the problem with the robustness of indirect comparison, such as the compatibility between the clinical studies of ravulizumab (301 and 302) and the clinical trial of eculizumab (TRIUMPH study).
- Conversely, because ravulizumab was pharmacologically similar to eculizumab and both drugs were determined to be noninferior in terms of efficacy, PBAC considered it reasonable to assume the superiority of ravulizumab to BSC in terms of efficacy.
- However, PBAC considered that there was uncertainty about the appropriateness or inappropriateness of assuming the superiority of eculizumab in terms of prognosis, which was shown in the previous evaluation of eculizumab versus BSC, in the evaluation of ravulizumab versus BSC, as well as about the degree of improvement in prognosis with ravulizumab versus BSC.
- The manufacturer performed CEA of ravulizumab versus eculizumab using the decision-tree model. For the analysis period of 1 year, ICER of ravulizumab versus eculizumab was estimated by considering the improvement in QOL resulting from the avoidance of transfusion and BTH and reduced costs of hospital visits due to ravulizumab.
- However, PBAC did not consider these results reliable because of the following reasons.
  - There was significant uncertainty about the estimation of disutility of transfusions because there were problems with the robustness of discrete choice experiment and the method used for mapping.
  - The assertion of the manufacturer that the incidence of BTH was lower in the ravulizumab group than in the eculizumab group was not supported, and the consideration of BTH in the model was not fully justified.
- The manufacturer performed CEA of ravulizumab versus BSC using the combination of partitioned survival analysis and the Markov model. The 3 states,

survival with PNH, survival with remission, and death, were considered for the model, and long-term outcomes were simulated over 55 years based on the data from a retrospective observational study. Consequently, the ICER of ravulizumab versus BSC was reported to be ≥AUD200,000/QALY.

- However, PBAC did not consider that the model of the manufacturer was useful for supporting decision making because it lacked face validity. In addition, PBAC pointed out some problems including inappropriate setting of improvement in prognosis associated with ravulizumab versus BSC.
- Sensitivity analysis showed that there was significant uncertainty in the ICER of ravulizumab versus BSC associated with the analysis period, survival curve, spontaneous remission rate, patient age, and utility weight settings, and the ICER was ≥AUD200,000/QALY in any of these cases.

2. Evaluation of additional benefit

2.1 Systematic review by the academic group

2.1.1 Clinical questions

To examine additional benefit of ravulizumab, a SR of randomized controlled trials by the academic group was performed based on the research questions as presented in Table 2-1. In the base case analysis, the target population was set as patients with PNH, intervention as ravulizumab, and the comparator as eculizumab. In the scenario analysis, the target population was set as patients with PNH, intervention as ravulizumab, and the comparator as BSC (symptomatic therapy other than complement inhibitor therapy). For each of the two research questions, a search formula was developed and a search using the designated databases was performed. The outcomes were efficacy and safety, and the period of search was from before the start of the phase III study of ravulizumab to the date of literature search.

Table 2-1 Research questions of SR by the academic analysis

Item	Base case analysis	Scenario analysis
Population	PNH	PNH
Intervention	Ravulizumab	Ravulizumab
Comparator	Eculizumab	Best supportive care (symptomatic therapy other than complement inhibitor therapy)
Outcome	Efficacy and safety	Efficacy and safety
Study design	Randomized controlled trial	Randomized controlled trial
Literature search period	January 2016 through January 2020	January 2016 through January 2020

2.1.2 Implementation flow

In the literature search operation, an expert of medical information service/literature search developed the search formula by combining conditions for disease name, drug name, study design, and search period. Screening based on publication abstracts and the following operation to identify relevant RCTs for the evaluation of additional benefit

were performed with blinding by 2 independent reviewers. Inclusion or exclusion of publications was determined on the basis of the prespecified inclusion and exclusion criteria, and inconsistencies between the reviewers occurring in the process of these operations were resolved through discussion by both reviewers. The RCTs identified were summarized in a table form with a summary of results.

2.1.3 Inclusion and exclusion criteria

The key inclusion and exclusion criteria for the SR are presented as follows.

<Inclusion criteria>

- The target disease is PNH.
- The intervention is ravulizumab.
- The comparator is eculizumab and BSC for the base case and scenario analyses, respectively.
- The study design is randomized controlled trial.
- Published during the designated period.

<Exclusion criteria>

- Abstract or meeting minutes
- Not written in English or Japanese

2.1.4 Database

PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of SRs, and Ichushi-Web were used for collection of the target studies.

2.1.5 Search formula

The search formulas for the SR for base case analysis are presented as follows.

Search formula for PubMed
Date of search: January 16, 2020

("Hemoglobinuria, Paroxysmal"[MH] OR "nocturnal hemoglobinuria"[TIAB] OR "paroxysmal hemoglobinuria"[TIAB] OR "marchiafava micheli"[TIAB]) AND ("ravulizumab"[NM] OR ravulizumab[TIAB] OR ultomiris[TIAB]) AND ("eculizumab"[NM] OR eculizumab[TIAB] OR soliris[TIAB] OR h5g1[TIAB]) AND ("Randomized Controlled Trial"[PT] OR ("randomized"[TI] AND (trial[TI] OR trials[TI])) OR "Randomized Controlled Trials as Topic"[MH]) AND("2016"[PDAT] : "3000"[PDAT])
Number of publications: 9

Search formula for Embase
Date of search: January 16, 2020
EMB.EXACT.EXPLODE("paroxysmal nocturnal hemoglobinuria") AND EMB.EXACT.EXPLODE("ravulizumab") AND EMB.EXACT.EXPLODE("eculizumab") AND (EMB.EXACT.EXPLODE("randomized controlled trial") OR ALL(random AND trial)) AND PD(2016-2020)
Number of publications: 15

Search formula for Cochrane
Date of search: January 16, 2020
#1 ("nocturnal hemoglobinuria"):ti,ab,kw OR (”paroxysmal hemoglobinuria”):ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [Hemoglobinuria, Paroxysmal] explode all trees
#3 #1 OR #2
#4 (ravulizumab):ti,ab,kw OR (ultomiris):ti,ab,kw (Word variations have been searched)
#5 (eculizumab):ti,ab,kw OR (soliris):ti,ab,kw OR (h5g1):ti,ab,kw (Word variations have been searched)
#6 #3 AND #4 AND #5 with Cochrane Library publication date from Jan 2016 to present
Number of publications: 10

Search formula for Ichushi
Date of search: January 16, 2020
(hemoglobinuria-paroxysmal/TH or hemoglobinuria/TI or "paroxysmal hemoglobinuria"/TI or "nocturnal hemoglobinuria"/TI or "marchiafava micheli"/TI or "marchiafava micheli"/TA) and (Ravulizumab/TH or ravulizumab/TA or ultomiris/TA or ravulizumab/TA or ravulizumab/TA) and (Eculizumab/TH or eculizumab/TA or eculizumab/TA or soliris/TA or eculizumab/TA) and

(DT=2016:2020 and PT=original article and PT=excluding case report and case)
Number of publications: 0

The search formulas for the SR for scenario analysis are presented as follows.

Search formula for PubMed
Date of search: January 16, 2020
("Hemoglobinuria, Paroxysmal"[MH] OR "nocturnal hemoglobinuria"[TIAB] OR "paroxysmal hemoglobinuria"[TIAB] OR "marchiafava micheli"[TIAB]) AND (“ravulizumab”[NM] OR ravulizumab[TIAB] OR ultomiris[TIAB]) AND ("Randomized Controlled Trial"[PT] OR ("randomized"[TI] AND (trial[TI] OR trials[TI])) OR "Randomized Controlled Trials as Topic"[MH]) AND ("2016"[PDAT] : "3000"[PDAT])
Number of publications: 9

Search formula for Embase
Date of search: January 16, 2020
EMB.EXACT.EXPLODE("paroxysmal nocturnal hemoglobinuria") AND EMB.EXACT.EXPLODE("ravulizumab") AND (EMB.EXACT.EXPLODE("randomized controlled trial") OR ALL(random AND trial)) AND PD(2016-2020)
Number of publications: 15

Search formula for Cochrane
Date of search: January 16, 2020
#1 ("paroxysmal nocturnal hemoglobinuria"):ti,ab,kw OR ("paroxysmal hemoglobinuria"):ti,ab,kw OR ("marchiafava micheli"):ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [Hemoglobinuria, Paroxysmal] explode all trees
#3 #1 OR #2
#4 (ravulizumab):ti,ab,kw OR (ultomiris):ti,ab,kw (Word variations have been searched)
#5 #3 #4 with Cochrane Library publication date from Jan 2016 to present
Number of publications: 10

Search formula for Ichushi
Date of search: January 16, 2020

(hemoglobinuria-paroxysmal/TH or hemoglobinuria/TI or "paroxysmal hemoglobinuria"/TI or "nocturnal hemoglobinuria"/TI or "marchiafava micheli"/TI or "marchiafava micheli"/TA) and (Ravulizumab/TH or ravulizumab/TA or ultomiris/TA or ravulizumab/TA or ravulizumab/TA) and (DT=2016:2020 and PT=original article and PT=excluding case report and case)
Number of publications: 0

2.1.6 Search results

The results of the SR were summarized as shown in Figure 2-1 with reference to the flow chart recommended by PRISMA Statement.

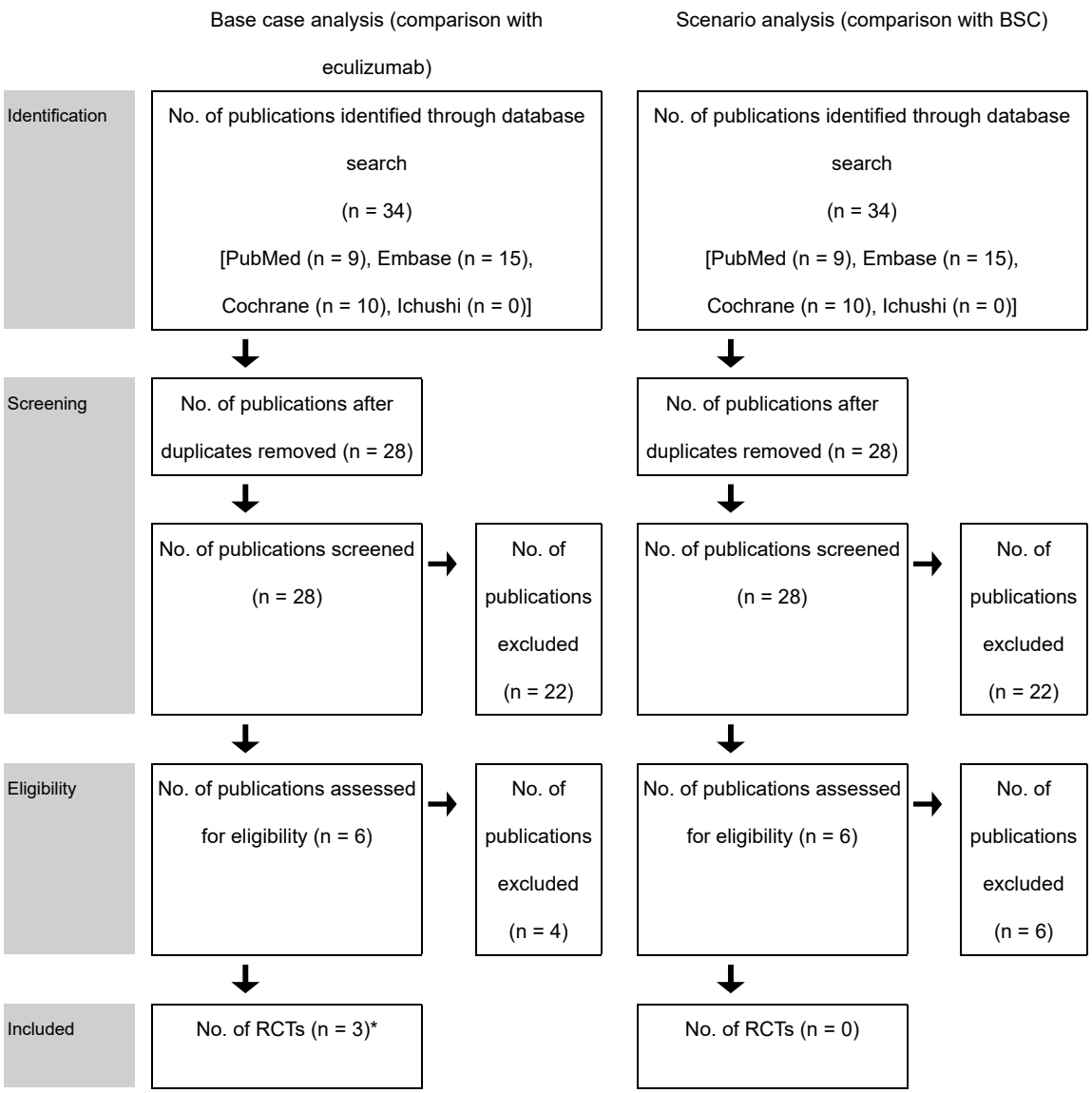


Figure 2-1 Flow chart of SR by the academic group

*One of the studies was identified through the process of monitoring new clinical studies, etc., published after completion of the SR.

<List of publications for the base case analysis>

(1) Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530-539.

(2) Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549.

(3) Ishiyama K, Nakao S, Usuki K, et al. Results from multinational phase 3 studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: subgroup analysis of Japanese patients. Int J Hematol. 2020;112(4):466-476.

The SR showed that the 2 studies, 301 and 302, were the RCTs that were relevant to the research questions for the base case analysis (comparison with eculizumab) ((1) and (2) in the list of publications for the base case analysis). In addition, 1 article on subgroup analysis of the Japanese populations in 301 and 302 was identified through the process of monitoring new clinical studies, etc., published after completion of the SR ((3) in the list of publications for the base case analysis). No randomized controlled study that was relevant to the research questions for the scenario analysis (comparison with BSC) could be found.

2.1.7 Summary of clinical trials

A summary of the 2 RCTs (301 and 302) that were relevant to the research questions for the base case analysis (comparison with eculizumab) is provided in Table 2-2. The results of subgroup analysis of the Japanese populations in 301 and 302 are also summarized in Table 2-2.

Table 2-2 List of literatures

Study name	ALXN1210-PNH-301 study[6]	ALXN1210-PNH-302 study[7]
Bibliographic information	Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530-539.	Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549.
Clinicaltrials.gov registry information	#NCT02946463	#NCT03056040
Study sites	Multicenter	Multicenter
Study enrollment period	December 2016 through January 2018	June 2017 through March 2018
Target population	Patients ≥18 years of age with PNH who are naive to complement inhibitors	Patients ≥18 years of age with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months
Eligibility criteria	· Male or female ≥18 years of age at the time of informed consent · PNH diagnosis confirmed using high-sensitivity flow cytometry · Presence of ≥1 PNH-related symptoms within 3 months before screening	· Male or female ≥18 years of age at the time of informed consent · Treated with eculizumab for at least 6 months prior to Day 1 · Presence of ≥1 PNH-related symptoms within 3 months before screening · LDH level ≤1.5 times the upper limit of normal at screening

	· LDH level ≥1.5 times the upper limit of normal at screening · Meningococcal vaccination within 3 years prior to, or at the time of, initiating study treatment · Female patients of childbearing potential and male patients with a female partner of childbearing potential need to follow the protocol-specified guidance to avoid pregnancy during treatment and for 8 months after the last study treatment.	· Meningococcal vaccination within 3 years prior to, or at the time of, initiating study treatment · Female patients of childbearing potential and male patients with a female partner of childbearing potential need to follow the protocol-specified guidance to avoid pregnancy during treatment and for 8 months after the last study treatment.
Key exclusion criteria	· Previous treatment with a complement inhibitor · Platelet count of <30,000/mm^3 or absolute neutrophil count of <500/μL at screening · History of bone marrow transplantation · Body weight of <40 kg at screening · History of meningococcal infection, history of unexplained recurrent infection, or history of active systemic bacterial, viral, or fungal infection within 14 days prior to initiating study treatment · A fever with a temperature of ≥38°C within 7 days prior to initiating study treatment · HIV infection · Participation in another clinical study before initiation of study treatment, or receipt of an investigational treatment and being within 30 days or 5 half-lives of the therapeutic	· An LDH level >2 times the ULN during the 6 months preceding Day 1 · A major adverse vascular event (MAVE) observed during the 6 months preceding Day 1 · Platelet count of <30,000/mm^3 or absolute neutrophil count of <500/μL at screening · History of bone marrow transplantation · Body weight of <40 kg at screening · History of meningococcal infection, history of unexplained recurrent infection, or history of active systemic bacterial, viral, or fungal infection within 14 days prior to initiating study treatment · A fever with a temperature of ≥38°C within 7 days prior to initiating study treatment · Presence of HIV infection

	drug used (whichever is longer) · Females who plan to become pregnant or are pregnant or breastfeeding · Females who have a positive pregnancy test result at screening or on Day 1	· Participation in another clinical study before initiation of study treatment, or receipt of an investigational treatment and being within 30 days or 5 half-lives of the therapeutic drug used (whichever is longer) · Females who plan to become pregnant or are pregnant or breastfeeding · Females who have a positive pregnancy test result at screening or on Day 1
Details of interventional method	· Ravulizumab (n = 125) · Weight-based dosing: An initial dose (Day 1) and maintenance doses (Day 15 and every 8 weeks thereafter) given · Treatment duration: 26 weeks *A loading dose on Day 1 (for patients weighing ≥40 and <60 kg, 2,400 mg; for patients weighing ≥60 and <100 kg, 2,700 mg; and for patients weighing ≥100 kg, 3,000 mg). Maintenance doses (for patients weighing ≥40 and <60 kg, 3,000 mg; for patients weighing ≥60 and <100 kg, 3,300 mg; and for patients weighing ≥100 kg, 3,600 mg)	· Ravulizumab (n = 97) · Weight-based dosing: A loading dose on Day 1 followed by maintenance doses of ravulizumab (Day 15 and every 8 weeks thereafter) · Treatment duration: 26 weeks *After the 4-week screening period, subjects were stratified according to transfusion history (the presence or absence of a history of pRBC transfusion during the year before initiating study treatment) and randomly assigned in a 1:1 ratio either to switch to ravulizumab (ravulizumab group) or continue eculizumab (eculizumab group). *Day 1 of ravulizumab therapy is 2 weeks after the last dose of eculizumab.

		*A loading dose on Day 1 (for patients weighing ≥40 and <60 kg, 2,400 mg; for patients weighing ≥60 and <100 kg, 2,700 mg; and for patients weighing ≥100 kg, 3,000 mg). Maintenance doses (for patients weighing ≥40 and <60 kg, 3,000 mg; for patients weighing ≥60 and <100 kg, 3,300 mg; and for patients weighing ≥100 kg, 3,600 mg)
Details of comparator	· Eculizumab (n = 121) · An induction dose of 600 mg (Days 1, 8, 15, and 22) and maintenance doses of 900 mg (Day 29 and every 2 weeks thereafter) · Treatment duration: 26 weeks	· Eculizumab (n = 98) · Maintenance doses of 900 mg (every 2 weeks) · Treatment duration: 26 weeks
Study design	Phase III, randomized	Phase III, randomized
Blinding method	Open-label	Open-label
Primary endpoint	· Proportion of achieving transfusion avoidance · Proportion of achieving normalization of LDH levels	Percent change in LDH
Key secondary endpoints	· Percent change in LDH · Change in total FACIT-Fatigue score · Proportion of patients with BTH	· Proportion of patients with BTH · Change in total FACIT-Fatigue score · Proportion of achieving transfusion avoidance

Efficacy	・ Proportion of achieving transfusion avoidance: 73.6% in the ravulizumab group and 66.1% in the eculizumab group. The between-group difference was 6.8% (95% CI: −4.66% to 18.14%) and the lower limit of the 95% CI was above −20%, the noninferiority margin, demonstrating the noninferiority of ravulizumab. ・ Proportion of achieving normalization of LDH levels: 53.6% in the ravulizumab group and 49.4% in the eculizumab group. The adjusted odds ratio for the ravulizumab group versus the eculizumab group was 1.187 (95% CI: 0.796 to 1.769) and the lower limit of the 95% CI was above 0.39, the noninferiority margin, demonstrating the noninferiority of ravulizumab. ・ Percent change in LDH: The least square mean percent change from baseline was −76.84% in the ravulizumab group and −76.02% in the eculizumab group, with the between-group difference of −0.83% (95% CI: −5.21% to 3.56%). ・ Proportion of patients with BTH: 4.0% (5/125 patients) in the ravulizumab group and 10.7% (13/121 patients) in the eculizumab group, with the between-group difference of −6.7% (95% CI: −14.21% to 0.18%).	・ Percent change in LDH: The least square mean change from baseline was −0.82% in the ravulizumab group and 8.39% in the eculizumab group. The between-group difference was −9.21% (95% CI: −18.84% to 0.42%) and the upper limit of the 95% CI was below 15%, demonstrating the noninferiority of ravulizumab. ・ Proportion of patients with BTH: 0% in the ravulizumab group and 5.1% (5/98 patients) in the eculizumab group, with the between-group difference of −5.1% (95% CI: −18.99% to 8.89%). ・ Proportion of achieving transfusion avoidance: 87.6% in the ravulizumab group and 82.7% in the eculizumab group, with the between-group difference of 5.5% (95% CI: −4.27% to 15.68%). ・ Total FACIT-Fatigue score: The least square mean change from baseline was 2.01 in the ravulizumab group and 0.54 in the eculizumab group, with the between-group difference of 1.47 (95% CI: −0.21 to 3.15).

	・ Total FACIT-Fatigue score: The least square mean change from baseline was 7.07 in the ravulizumab group and 6.40 in the eculizumab group, with the between-group difference of 0.67 (95% CI: −1.21 to 2.55).	
Safety	・ Incidence rate of adverse reactions: 40.8% (51/125 patients) in the ravulizumab group and 41.3% (50/121 patients) in the eculizumab group	・ Incidence rate of adverse reactions: 24.7% (24/97 patients) in the ravulizumab group and 14.3% (14/98 patients) in the eculizumab group
Efficacy in the Japanese population[8]	・ The ravulizumab group, 18 patients; the eculizumab group, 15 patients ・ Proportion of achieving transfusion avoidance: 83.3% in the ravulizumab group and 53.3% in the eculizumab group, with the between-group difference of 30.0% (95% CI: −4.56% to 59.60%). ・ Proportion of achieving normalization of LDH levels: 52.1% in the ravulizumab group and 60.2% in the eculizumab group, with the between-group difference of 0.719% (95% CI: 0.158% to 3.267%). ・ Proportion of patients with BTH: There were no patients with BTH in both groups.	・ The ravulizumab group, 5 patients; the eculizumab group, 7 patients ・ Percent change in LDH: The percent change from baseline was 8.34% in the ravulizumab group and 15.77% in the eculizumab group, with the between-group difference of −7.42% (95% CI: −21.85% to 7.01%). ・ Proportion of patients with BTH: There were no patients with BTH in both groups. ・ Proportion of achieving transfusion avoidance: 80.0% in the ravulizumab group and 57.1% in the eculizumab group, with the between-group difference of 22.9% (95% CI: −36.23% to 71.64%).

Safety in the Japanese population[8]	・ Incidence of adverse reactions: 94.4% (17/18 patients) in the ravulizumab group and 93.3% (14/15 patients) in the eculizumab group	・ Incidence of adverse reactions: 100% (5/5 patients) in the ravulizumab group and 85.7% (6/7 patients) in the eculizumab group

2.2 Summary of additional benefit assessment by the manufacturer and review results

The methodology of the SR performed by the manufacturer to examine additional benefit of ravulizumab was generally appropriate. Through the SR, the manufacturer identified the following 6 publications related to the RCTs to evaluate the efficacy and safety of ravulizumab (301 and 302).

(1) Alexion Pharmaceuticals. Academic in confidence. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naïve adult patients with PNH. Clinical study report. 2018.
(2) Alexion Pharmaceuticals. Academic in confidence. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab. Clinical study report. 2018.
(3) Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530-539.
(4) Brodsky RA, De Latour RP, Rottinghaus ST, et al. A Prospective Analysis of Breakthrough Hemolysis in 2 Phase 3 Randomized Studies of Ravulizumab (ALXN1210) Versus Eculizumab in Adults with Paroxysmal Nocturnal Hemoglobinuria. Paper presented at: American Society of Hematology2018; San Diego, CA.
(5) Weitz IC, Kulagin A, Nakao S, et al. A Phase 3 Study of Ravulizumab (ALXN1210) Versus Eculizumab in Adults with Paroxysmal Nocturnal Hemoglobinuria Naive to Complement Inhibitors: Results of a Subgroup Analysis with Patients Stratified by Baseline Hemolysis Level, Transfusion History, and Demographics. Paper presented at: American Society of Hematology2018; San Diego, CA.
(6) Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549.

Publications (1) and (2) were clinical study reports of the manufacturer that were available from the clinicaltrials.gov registry information. Publications (3) and (6) were the original article about 301 and 302, respectively, and identical to the publications identified by the academic analysis. Publications (4) and (5), which were records of

presentation at a scientific meeting, were determined to be excluded because they met the exclusion criteria for the SR of the academic analysis (“Abstract or meeting minutes”). Through the monitoring of new clinical studies, etc., performed after the SR of the academic analysis, 1 original article on subgroup analysis of the Japanese populations in 301 and 302 was identified in addition to the following 6 publications[8].

The manufacturer used the following three outcome measures for the evaluation of additional benefit: reduction in the incidence rate of free C5-related BTH, transfusion avoidance, and improvement in QOL associated with extended dosing intervals.

<Reduction in free C5-related BTH>

In 301 and 302, the occurrence of BTH was defined as “the observation of ≥1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin <10 g/dL], MAVEs [including thrombosis], dysphagia, or erectile dysfunction) in the presence of LDH ≥2 times the upper limit of normal after on-treatment reduction of LDH to <1.5 times the upper limit of normal.”

However, free C5-related BTH came from the additional analysis of the proportion of patients with BTH, an endpoint prespecified for 301 and 302[6, 7] and the use of free C5 testing is rare in actual clinical settings; therefore, its appropriateness as a measure for additional benefit assessment is unclear[9]. According to HTA agencies in other countries, it was pointed out that because 301 and 302 were open-label studies, the possibility of information bias and detection bias could not be ruled out in efficacy and safety evaluations using such an endpoint.

<Transfusion avoidance>

Transfusion avoidance was set as the primary endpoint for 301 and as a secondary endpoint for 302[6, 7]. In both studies, transfusion avoidance was defined as “the proportion of subjects who remained transfusion-free and did not require a transfusion per protocol-specified guidelines during the study period up to Day 183 (Week 26)”. Whether a subject required a transfusion or not was based on “a hemoglobin level ≤9 g/dL with signs or symptoms of sufficient severity to warrant transfusion or a hemoglobin level ≤7 g/dL regardless of the presence of signs or symptoms.”

According to HTA agencies in other countries, it was pointed out that because 301 and 302 were open-label studies, the possibility of information bias and detection bias could

not generally be ruled out in efficacy and safety evaluations using such an endpoint.

<Improvement in QOL associated with extended dosing intervals>

Improvement in QOL associated with extended dosing intervals was not included in the endpoints set for 301 and 302, and no reports have been presented of demonstration of the improvement in the relevant patient population.

2.3 Results of additional benefit assessment

An additional benefit of ravulizumab was evaluated on the basis of the report by the manufacturer, the SR by the academic group, and other information including the additional literature review conducted as necessary. The results of the evaluation are presented in Tables 2-3, 2-6, and 2-7.

Table 2-3 Additional benefit assessment (reduction in free C5-related BTH)

Target population	Paroxysmal nocturnal hemoglobinuria
Intervention	Ravulizumab
Comparator	Eculizumab
Outcome	Reduction in free C5-related BTH
Presence or absence of additional benefit	□ With additional benefit ■ “No additional benefit” or “Cannot be determined”
Data serving as the rationale for judgment	□ Meta-analysis of RCTs ■ Single RCT (2 RCTs) □ Prospective, controlled, observational study □ Indirect comparison of RCTs □ Comparison of single-arm studies □ No relevant clinical study data □ Other
Reason for judging the presence or absence of additional benefit	Although ravulizumab was shown to be noninferior in the two RCTs to evaluate the efficacy and safety of ravulizumab (301 and 302), the elevation of free C5 levels to ≥0.5 μg/mL and the occurrence of free C5-related BTH, which were observed in the eculizumab group, were not observed in the ravulizumab group. Consequently, the manufacturer asserted that there was additional benefit of ravulizumab on reduction in the incidence rate of free C5-related BTH[10]. However, it cannot be concluded that additional benefit of ravulizumab was shown because of the following. (1) The results of 301 and 302 did not demonstrate that ravulizumab was superior to eculizumab in terms of the incidence rate of BTH including free C5-related BTH with a statistically significant difference[6, 7].

	(2) Free C5-related BTH came from the additional analysis of the proportion of patients with BTH, a prespecified endpoint, and the use of free C5 testing is rare in actual clinical settings; therefore, its appropriateness as a measure for the evaluation of additional benefit is unclear[9]. (3) Ravulizumab therapy is given with dose adjustments in consideration of patient's body weight (a dose is set for each of the following three categories of patient's body weight: 40–60 kg, 60–100 kg, and ≥100 kg)[11]. By contrast, eculizumab therapy is given at a fixed dose independent of patient's body weight[12]. Therefore, the possibility of insufficient doses of eculizumab in patients with a higher body weight resulting in the higher incidence of free C5-related BTH in the eculizumab group cannot be ruled out. Actually, detailed examination of the data of 301 and 302 showed that the populations <60 kg had no free C5-related BTH, suggesting that free C5-related BTH occurred in patients with a higher body weight (Tables 2-5 and 2-6 and Figures 2-2, 2-3, 2-4, and 2-5)[13]. As a reference, the mean body weight of the Japanese population was 58.1 kg at the time of the initial dose in the post-marketing surveillance.

Table 2-4 Relationship of body weight with breakthrough hemolysis in 301 study

	Ravulizumab arm N = 125	Eculizumab arm N = 121
Number of patients with breakthrough hemolysis	5/125 (0/125)	13/121 (7/121)
<60 kg	2/41 (0/41)	3/38 (0/38)
≥60 kg	3/84 (0/84)	10/83 (7/83)
Number of patients with free C5-related breakthrough hemolysis	0/125 (0/125)	5/121 (5/121)
<60 kg	0/41 (0/41)	0/38 (0/38)
≥60 kg	0/84 (0/84)	5/83 (5/83)

The number of patients with insufficient blood concentrations of the drug is indicated in parentheses. The table was prepared on the basis of the report on the occurrence

status of adverse events in the individual cases in 301[13].

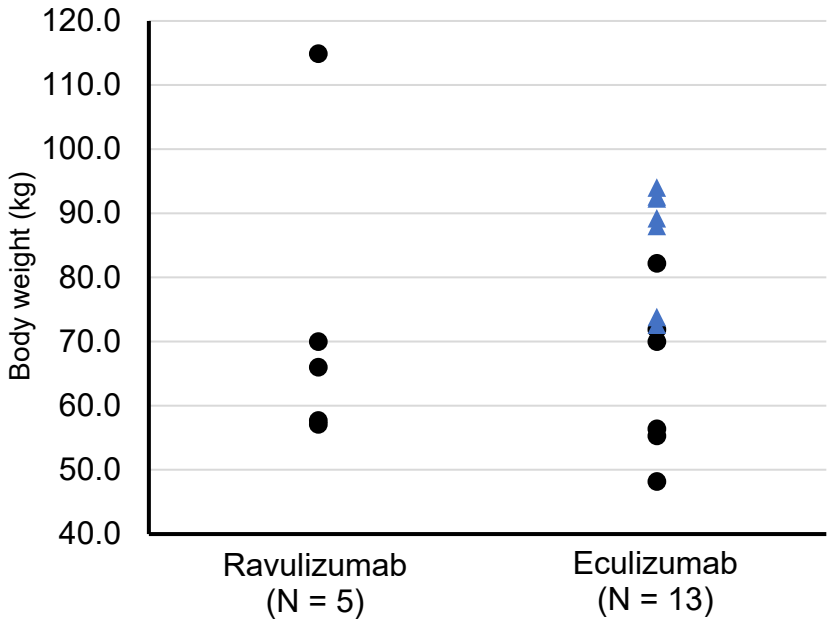


Figure 2-2 Body weight distribution in patients with breakthrough hemolysis (301 study)

▲ denotes patients with insufficient blood concentrations of the drug.

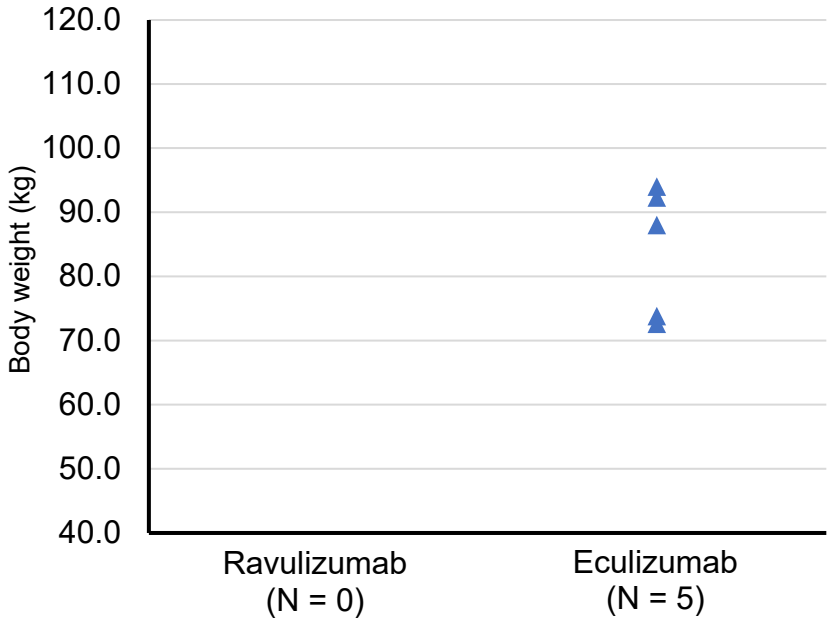


Figure 2-3 Body weight distribution in patients with free C5-related breakthrough hemolysis (301 study)

▲ denotes patients with insufficient blood concentrations of the drug.

Table 2-5 Relationship of body weight with breakthrough hemolysis in 302 study

	Ravulizumab arm N = 97	Eculizumab arm N = 98
Number of patients with breakthrough hemolysis	0/97 (0/97)	5/98 (2/98)
<60 kg	0/27 (0/27)	0/22 (0/22)
≥60 kg	0/70 (0/70)	5/76 (2/76)
Number of patients with free C5-related breakthrough hemolysis	0/97 (0/97)	2/98 (2/98)
<60 kg	0/27 (0/27)	0/22 (0/22)
≥60 kg	0/70 (0/70)	2/76 (2/76)

The number of patients with insufficient blood concentrations of the drug is indicated in parentheses. The table was prepared on the basis of the report on the occurrence status of adverse events in the individual cases in Study 302[13].

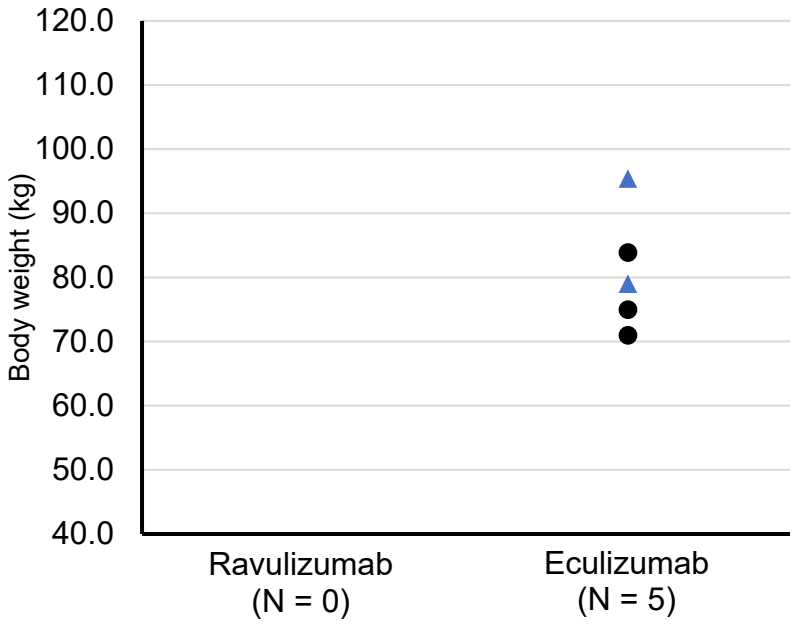


Figure 2-4 Body weight distribution in patients with breakthrough hemolysis (302 study)

▲ denotes patients with insufficient blood concentrations of the drug.

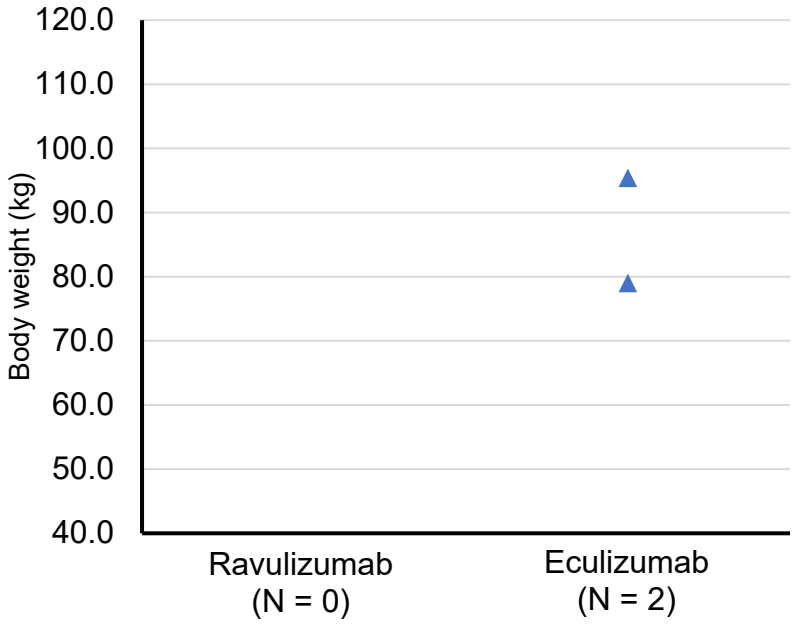


Figure 2-5 Body weight distribution in patients with free C5-related breakthrough hemolysis (Study 302)

▲ denotes patients with insufficient blood concentrations of the drug.

Table 2-6 Additional benefit assessment (transfusion avoidance)

Target population	Paroxysmal nocturnal hemoglobinuria
Intervention	Ravulizumab
Comparator	Eculizumab
Outcome	Transfusion avoidance
Presence or absence of additional benefit	□ With additional benefit ■ "No additional benefit" or "Cannot be determined"
Data serving as the rationale for judgment	□ Meta-analysis of RCTs ■ Single RCT (2 RCTs) □ Prospective, controlled, observational study □ Indirect comparison of RCTs □ Comparison of single-arm studies □ No relevant clinical study data □ Other
Reason for judging the presence or absence of additional benefit	Transfusion avoidance was significantly higher in the ravulizumab group than in the eculizumab group in the two RCTs to evaluate the efficacy and safety of ravulizumab (301 and 302). Consequently, the manufacturer asserted that there was additional benefit of ravulizumab on transfusion avoidance[10]. However, it cannot be concluded that additional benefit of ravulizumab was shown because of the following. (1) The results of 301 and 302 did not demonstrate that ravulizumab was superior to eculizumab in terms of the frequency of transfusion with a statistically significant difference[6, 7]. (2) HTA agencies in other countries, etc., pointed out that information bias may be introduced in an open-label study with the use of an endpoint such as transfusion.

Table 2-7 Additional benefit assessment (improvement in QOL associated with extended dosing intervals)

Target population	Paroxysmal nocturnal hemoglobinuria
Intervention	Ravulizumab
Comparator	Eculizumab
Outcome	Improvement in QOL associated with extended dosing intervals
Presence or absence of additional benefit	□ With additional benefit ■ “No additional benefit” or “Cannot be determined”
Data serving as the rationale for judgment	□ Meta-analysis of RCTs ■ Single RCT (2 RCTs) □ Prospective, controlled, observational study □ Indirect comparison of RCTs □ Comparison of single-arm studies □ No relevant clinical study data ■ Other (investigation using a discrete choice experiment in the general population)
Reason for judging the presence or absence of additional benefit	On the basis of the finding that an investigation using a discrete choice experiment in overseas general population showed that utility weights can be expected to improve with a reduction in dosing frequency from that at 2-week intervals assumed for eculizumab therapy to that at 8-week intervals assumed for ravulizumab, the manufacturer asserted that there was additional benefit of ravulizumab on improvement in QOL associated with extended dosing intervals[10, 14]. However, it cannot be concluded that additional benefit of ravulizumab was shown because of the following. (1) The result of the investigation based on a discrete choice experiment was not relevant to patients but came from an investigation of preferences of the general population. Therefore, it is not an appropriate outcome measure for the evaluation of additional benefits. (2) No reports on the demonstration of improvement in utility weights associated with extended dosing intervals in patients with PNH in clinical studies have been reported to date. (3) The manufacturer performed statistical analysis using a linear mixed model by mapping EORTC QLQ-C30 scores in 301 and 302 to EQ-5D. However, the statistical analysis did not show that ravulizumab was superior to eculizumab in terms of utility weights

	with a statistically significant difference[10].

On the basis of the results of additional benefit assessment, it is appropriate to perform cost-effectiveness evaluation of ravulizumab as shown in Table 2-8.

Tale 2-8 Results of the evaluation of additional benefit and the methodology of cost-effectiveness evaluation

Population	Paroxysmal nocturnal hemoglobinuria
Target product	Ravulizumab
Comparator	Eculizumab
Results of additional benefit assessment	**<Reduction in free C5-related BTH>** It cannot be concluded that additional benefit was shown. **<Transfusion avoidance>** It cannot be concluded that additional benefit was shown. **<Improvement in QOL associated with extended dosing intervals>** It cannot be concluded that additional benefit was shown.
Method of cost-effectiveness evaluation	Cost-minimization analysis
Sensitivity analysis (Scenario analysis)	A conventional therapy (BSC) except for eculizumab can be the comparator technology for “patients who have an indication for eculizumab therapy but remain untreated.” However, because the number of relevant patients was expected to be limited and there might be uncertainty in the analysis, it was considered to perform the cost-effectiveness analysis not by base case analysis but by sensitivity analysis (scenario analysis).

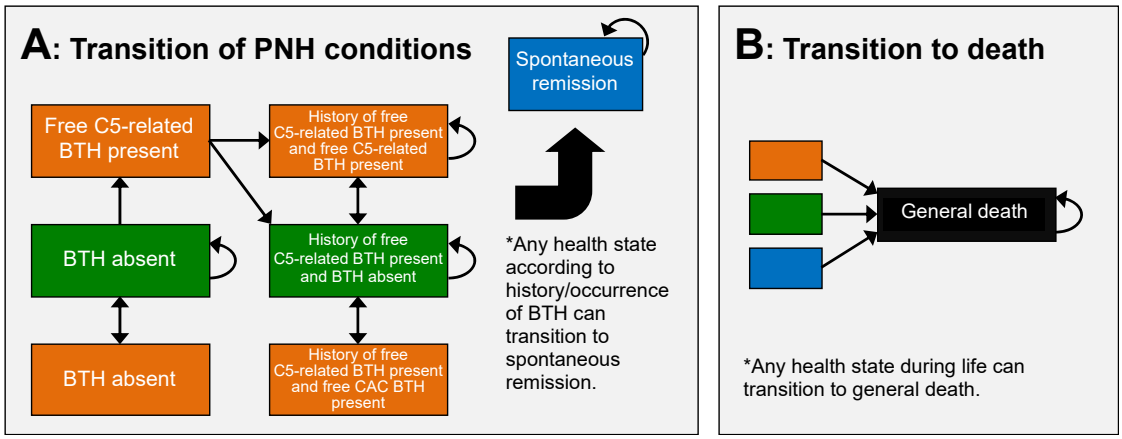
3. Evaluation of cost-effectiveness

3.1 Summary of manufacturer's results and review by academic group

3.1.1 Summary of CEA compared to eculizumab

The manufacturer performed the cost-effectiveness analysis assuming that there was additional benefit of ravulizumab over eculizumab on reduction in the incidence rate of free C5-related BTH, transfusion avoidance, and improvement in QOL associated with extended dosing intervals. In the cost-effectiveness analysis, a Markov model of 8 health states including death was used (Figure 3-1)[10]. The patient age was 55.6 years at the start of the analysis, and the upper limit of age for analysis was set at 100 years. An annual discount rate of 2% was applied to costs and effects[10]. The costs, effects, and ICER were estimated for each treatment group by cohort simulation. The main assumptions in the model used for analysis were as follows[10].

- No free C5-related BTH occurs during treatment with ravulizumab.
- Patients with a history of BTH have an increased incidence rate of BTH thereafter.
- The incidence rate of the first free C5-related BTH decreases after a certain period of time from the initiation of analysis.
- The risk of death in each treatment group is comparable with that in the general population.
- The occurrences of free C5-related BTH and CAC BTH have no effect on the risk of death.
- Red blood cell transfusion does not occur twice or more in 1 cycle.



Orange denotes health states of PNH with BTH, green denotes health states of PNH without BTH, and blue denotes the health state of spontaneous remission.

Figure 3-1 Model structure of the manufacturer[10]

The additional benefit of ravulizumab on reduction in the incidence rate of free C5-related BTH, transfusion avoidance, and improvement in QOL associated with extended dosing intervals was reflected on the following settings in the model[10].

(1) Set a certain difference in the incidence rate of free C5-related BTH (assume that the incidence rate is 0 in the ravulizumab group whereas it occurs at a certain rate in the eculizumab group).

(2) Set a certain difference in the rate of transfusion and transfusion volume (set values based on the data of each treatment group in 301 study).

(3) Set a certain difference in baseline utility weight (assuming improvement in QOL associated with extended dosing intervals, calculate the utility weight for the ravulizumab group at a premium of 0.069 over the utility weight for the eculizumab group).

The results of the base case analysis were summarized as shown in Tables 3-1–3-3[10].

Table 3-1 Results of base case analysis of CEA by the manufacturer

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Ravulizumab	19.86	1.25	855,544,150	8,892,169	7,109,296

Eculizumab	18.61		846,651,981		

Table 3-2 Breakdown of estimated QALY by health state (reported by the manufacturer)

Health state	Ravulizumab	Eculizumab
Spontaneous remission	3.89	3.89
BTH absent	15.97	11.05
Free C5-related BTH present	0.00	0.01
CAC BTH present	0.01	0.00
History of free C5-related BTH present and BTH absent	0.00	3.64
History of free C5-related BTH present and free C5-related BTH present	0.00	0.02
History of free C5-related BTH present and free CAC BTH present	0.00	0.00
Total	19.86	18.61

Table 3-3 Breakdown of estimated costs by item (reported by the manufacturer)

Item	Ravulizumab (JPY)	Eculizumab (JPY)	Cost difference (JPY)
Acquisition cost	853,396,454	841,774,241	11,622,213
Management cost	1,375,533	3,655,765	−2,280,232
Treatment cost for BTH	23,084	104,207	−81,123
Cost of transfusion	728,885	1,097,575	−368,690
Cost of vaccines	20,194	20,194	0
Total	855,544,150	846,651,981	8,892,169

3.1.2 Summary of CEA compared to BSC

The manufacturer performed scenario analysis for the case in which the comparator technology is changed to BSC using the model in Figure 3-1. With the assumption that "*It is considered that patients receiving BSC therapy, who are not receiving ravulizumab or eculizumab, an anti-complement C5 antibody, have high concentrations of free C5 in blood all the time and thereby suffer frequent free C5-related BTH. Therefore, only the health state 'history of free C5-related BTH present and free C5-related BTH present' was considered as the PNH condition for the scenario analysis, which could transition to*

either 'spontaneous remission' or 'general death,' " the manufacturer performed the analysis with the following changes in the settings[10].

(1) Patients in the BSC group remain in the state "history of free C5-related BTH present and free C5-related BTH present."
(2) Transfusion occurs constantly in patients in the BSC group.
(3) The risk of death is higher in patients in the BSC group than in the general population. (Hazard ratio for general death rate is 4.76.)
(4) No drug acquisition or management cost is incurred in the BSC group.

The results of the scenario analysis by comparison with BSC were summarized as shown in Tables 3-4–3-6[10].

Table 3-4 Results of scenario analysis of CEA by the manufacturer

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Ravulizumab	19.86	8.05	855,544,150	819,004,596	101,700,385
BSC	11.81		36,539,554		

Table 3-5 Breakdown of estimated QALY by health state (reported by the manufacturer)

Health state	Ravulizumab	BSC
Spontaneous remission	3.89	3.09
BTH absent	15.97	0.00
Free C5-related BTH present	0.00	0.00
CAC BTH present	0.01	0.00
History of free C5-related BTH present and BTH absent	0.00	0.00
History of free C5-related BTH present and free C5-related BTH present	0.00	8.72
History of free C5-related BTH present and free CAC BTH present	0.00	0.00
Total	19.86	11.81

Table 3-6 Breakdown of estimated costs by item (reported by the manufacturer)

Item	Ravulizumab (JPY)	BSC (JPY)	Cost difference (JPY)
Acquisition cost	853,396,454	0	853,396,454
Management cost	1,375,533	0	1,375,533
Treatment cost for BTH	23,084	26,995,823	−26,972,740
Cost of transfusion	728,885	9,543,731	−8,814,846
Cost of vaccines	20,194	0	20,194
Total	855,544,150	36,539,554	819,004,596

3.1.3 Issues on CEA compared to eculizumab

The manufacturer performed the cost-effectiveness analysis assuming additional benefit of ravulizumab over eculizumab on reduction in the incidence rate of free C5-related BTH, transfusion avoidance, and improvement in QOL associated with extended dosing intervals. However, it cannot be concluded that the results of additional benefit assessment showed any additional benefit on any of the outcome measures. Therefore, it is inappropriate to perform a cost-effectiveness analysis, and it is appropriate to perform a cost-minimization analysis assuming that there is no difference between the treatment effects of ravulizumab and eculizumab.

< Issues on the model used for CEA>

In the cost-effectiveness analysis of ravulizumab, the manufacturer estimated long-term outcomes in patients with PNH using a Markov model of 8 health states including death (Figure 3-1). Although in recent years there have been original articles published on cost-effectiveness analyses using a similar model structure, the following issues are found regarding structural uncertainty in the model[15].

- Free C5-related BTH came from the additional analysis of the proportion of patients with BTH, a prespecified endpoint, and the use of free C5 testing is rare in actual clinical settings; therefore, its appropriateness as a measure for the evaluation of therapeutic effect is unclear[9].
- The increased risk of subsequent free C5-related BTH in patients with a history of BTH is not fully justified. The data submitted by the manufacturer show an increasing tendency in terms of point estimates, but with no statistical difference, etc., suggesting uncertainty[10].

<Issues on the setting for BTH>

The manufacturer estimated the incidence rate of BTH in each treatment group using the data of the post-marketing surveillance of eculizumab. However, the setting of a certain difference in the incidence rate of BTH between ravulizumab and eculizumab is inappropriate because of the following issue.

- It was not demonstrated that ravulizumab was superior to eculizumab in terms of the incidence rate of BTH with a statistically significant difference.

<Issues on the setting for transfusion>

The manufacturer performed the cost-effectiveness analysis based on the data of the rate of transfusion and transfusion volume in 301 study. However, the setting of a certain difference in the rate of transfusion and transfusion volume between ravulizumab and eculizumab is inappropriate because of the following issues.

- It was not demonstrated that ravulizumab was superior to eculizumab in terms of the proportion of transfusion with a statistically significant difference.
- No statistically significant difference in transfusion volume was demonstrated between the treatment groups.

<Issues on the improvement in utility weight associated with extended dosing intervals>

The manufacturer performed the cost-effectiveness analysis assuming that utility weights can be expected to improve with a reduction in dosing frequency from that at 2-week intervals assumed for eculizumab therapy to that at 8-week intervals assumed for ravulizumab. More specifically, improvement in utility weights associated with extended dosing frequency was estimated by applying a mixed logit model using treatment selection (ravulizumab and eculizumab) as an objective variable and 5 attributes (life expectancy, dosing frequency, meningococcal infection, symptoms, and transfusion) as explanatory variables to the data of the discrete choice experiment (DCE) in overseas general population (Sweden)[14]. On the basis of these results, the baseline utility weights for the ravulizumab group was calculated using the setting that a premium of 0.069 is given over the baseline utility weights for the eculizumab group[14]. However, it is inappropriate to consider improvement in utility weights associated with extended dosing intervals for the ravulizumab group because of the following issues.

- No reports on the demonstration of improvement in utility weights associated with extended dosing intervals in patients with PNH in clinical studies have been reported to date.

- The manufacturer performed statistical analysis using a linear mixed model by mapping EORTC QLQ-C30 scores in 301 and 302 to EQ-5D. However, the statistical analysis did not show that ravulizumab was superior to eculizumab in terms of utility weights with a statistically significant difference[10].
- The DCE submitted by the manufacturer is for an investigation of preferences of overseas general population (Sweden) and does not necessarily reflect the preferences of the Japanese population. Particularly, the number of hospital/clinic visits per citizen is 2.7 in Sweden, whereas it is 12.6 in Japan, showing a substantial difference[16]. Therefore, the possibility that the improvement in utility weights associated with decreased dosing frequency was overestimated in the Japanese population cannot be ruled out. Even supposing that a difference is observed in utility weight, there is no basis for saying that the difference is maintained throughout life.

<Issues on the cost parameters>

To estimate management cost for the ravulizumab and eculizumab groups and the cost of thrombosis testing when BTH occurs, the manufacturer calculated the relevant costs using a commercial claims database. The medical information database (EBM provider®) provided by Medical Data Vision Co., Ltd. (MDV), including medical data and DPC data, which had been established with the authorization for secondary use obtained from DPC hospitals was used as the data source[10]. However, the following points need to be noted.

- The description of the extraction conditions for analysis objects (PNH and BTH testing) is insufficient, and the appropriateness of the definition of PNH for the claims is unclear.
- Regarding the estimated number of patients affected by PNH (the number of patients who had Specific Medical Expenses Recipient Certificate for PNH as of the end of fiscal year 2018, 764), the number of patients with PNH who visited hospitals from April 2016 to December 2019 extracted from the EBM provider (DPC claims data relevant to approximately 24% [413 institutions] of the national DPC hospitals are registered as of June 2020) was 102; however, it lacks data from an existing epidemiological study, etc., that allow examination of the representativeness of data, and the representativeness is unclear.
- There is uncertainty about the appropriateness of the cost items adopted for the analysis of claims data. More specifically, no sufficient data that allow examination

of the comprehensiveness of management cost (outpatient medical treatment) items that should be considered and the appropriateness of adoption or non-adoption for the cost items excluded as infrequently used medical treatments were presented by the manufacturer.

- Sensitivity analysis was performed to examine the effect of uncertainty in the aforementioned cost parameters; however, a variation range of ±20% was set across them and its appropriateness is unclear.

3.1.4 Issues on CEA compared to BSC

The manufacturer performed the scenario analysis by comparison with BSC assuming that in the BSC group patients in the virtual cohort are alive with constant free C5-related BTH unless they die or achieve spontaneous remission. However, no sufficient rationale to justify this assumption was presented. Therefore, caution is required in the interpretation of the scenario analysis by comparison with BSC performed by the manufacturer.

In the scenario analysis by comparison with BSC, the manufacturer assumed that the hazard ratio for death in the BSC group versus the general population was 4.76 based on an epidemiological study[10]. However, the following points need to be noted.

- The epidemiological study cited by the manufacturer involved a comparison of clinical courses of patients with PNH in Japan and the United States; however, it did not include any description of hazard ratio for death for the patients versus the general population, showing no rationale for the estimation of 4.76[17].

However, it is possible to consider analyses based on the value of hazard ratio as used by the manufacturer because of the following reasons.

- A registry study in patients with PNH in Korea reported that mortality was 4.81 times higher in patients with PNH with hemolysis prior to the launch of eculizumab (LDH ≥1.5 × ULN) than in the general population (standardized mortality ratio compared with the general population matched for age and sex: 4.81 [95% CI: 3.03 to 6.59])[18].
- A retrospective study in patients with PNH in the U.K. reported that the hazard ratio for patients treated versus untreated with eculizumab was 0.21 [95% CI: 0.05 to 0.88] (on the basis of the interpretation of the reciprocal of the reported value as the hazard ratio for patients untreated versus treated with eculizumab, it

is calculated as 1/0.21 = 4.762)[19].

In the scenario analysis by comparison with BSC, the manufacturer included only the treatment cost for BTH and the cost of transfusion in the calculation without considering the occurrence of drug acquisition and management costs in the BSC group. In a previous study regarding cost-effectiveness analysis of eculizumab, the occurrence of additional costs was considered for the cost items of treatment related to renal complications, Warfarin therapy, and treatment cost related to thrombotic events in the BSC group but not in the eculizumab group[20]. Therefore, the costs might have been underestimated in the BSC group in the submitted model, and caution is required in the interpretation of the scenario analysis by comparison with BSC performed by the manufacturer.

3.2 Summary of revisions by academic group

On the basis of the results of additional benefit assessment by academic group, the following revised analysis of cost-effectiveness evaluation needs to be performed.

<Base case analysis>

- Perform a cost-minimization analysis, assuming that effects are similar between the therapies, because it cannot be concluded that an additional benefit of ravulizumab over eculizumab was shown.
- For the cost-minimization analysis, compare the total of drug acquisition and management costs between the ravulizumab and eculizumab groups, assuming that the consumption of medical resources other than the acquisition and management costs is the same between the groups.

<Sensitivity analysis (Scenario analysis)>

- Regarding the scenario analysis by comparison with BSC, the analyses submitted by the manufacturer were accepted in spite of the various limitations in them.

3.3 Methods of revised analysis

Table 3-7 Corresponding part of report by manufacturer

In the reports, etc. submitted by the manufacturer		
Section	Page	Starting line number (or table/figure number)
4. Details of analytical methods	P37 to 44	-

<Description of the report>

Omitted

< Details of academic analysis (revision)>

It cannot be concluded that the additional benefit assessment of ravulizumab showed any additional benefit on any of the outcome measures. Therefore, it is inappropriate to perform a cost-effectiveness analysis, and it is appropriate to perform a cost-minimization analysis assuming that there is no difference between the treatment effects of ravulizumab and eculizumab.

In the revised analysis, the estimated drug acquisition and management costs were compared between the ravulizumab and eculizumab groups, assuming that the consumption of medical resources other than the acquisition and management costs was the same between the groups.

The acquisition cost of ravulizumab was estimated in consideration of the body weight distribution in the Japanese population because the dose of ravulizumab was adjusted according to the patient's body weight. The body weight distribution in the Japanese population was set on the basis of the data from the post-marketing surveillance of eculizumab, which were used for the calculation of ravulizumab price (Table 3-8).

Table 3-8 Patient body weight distribution in the post-marketing surveillance of eculizumab (provided by the manufacturer)

Body weight group	No. of patients	Proportion of patients
[redacted]		

Body weight group	No. of patients	Proportion of patients
[redacted]		

*1 [redacted]

*2 [redacted]

In the same way as the drug prices and calculation method in the model of the manufacturer, the drug acquisition and management costs incurred every 2 weeks were considered. The unit price settings for the costs are presented in Table 3-9.

Table 3-9 Unit costs

Item	Unit price (JPY)	Amount per vial (mg)
Price of ravulizumab (JPY/vial)	730,894	300
Management cost of ravulizumab (JPY/dose)	11,761	-
Price of eculizumab (JPY/vial)	604,716	300
Management cost of eculizumab (JPY/dose)	7,856	-

The drug dose settings are presented in Table 3-10. The usual starting dose of ravulizumab is 2,400–3,000 mg, followed by 3,000–3,600 mg/dose (loading dose) after 2 weeks of the initial dose, and 3,000–3,600 mg/dose (maintenance doses) every 8 weeks thereafter, which are administered via intravenous infusion in consideration of the patient's body weight. The dose of eculizumab is started at 600 mg/dose and

administered via intravenous infusion for a total of 4 doses including the initial dose (loading doses) at once-weekly intervals, followed after a 1-week interval (4 weeks after the initial dose) by 900 mg/dose administered via intravenous infusion at subsequent intervals of 2 weeks (maintenance doses).

In the analysis, the relevant analyses were performed with the settings (a)–(d) presented as follows.

(a) Estimation of costs for the 8 weeks of maintenance doses

For simplification, drug acquisition and management costs were estimated for the 8 weeks of maintenance dose period assuming patients receiving long-term complement inhibitor therapy.

(b) Estimation of costs including the loading dose cost for the lifetime

Drug acquisition and management costs were estimated for patients in the virtual cohort in the analysis model of the manufacturer from the starting age of 55.62 to 100 years.

(c) Estimation of costs including the loading dose cost for the lifetime in consideration of discount rate

Drug acquisition and management costs were estimated for patients in the virtual cohort in the analysis model of the manufacturer from the starting age of 55.62 to 100 years. An annual discount rate of 2% was applied to the cost calculation.

(d) Estimation of costs including the loading dose cost for the lifetime in consideration of discount and survival rates

Drug acquisition and management costs were estimated for patients in the virtual cohort in the analysis model of the manufacturer from the starting age of 55.62 to 100 years. An annual discount rate of 2% was applied to the cost calculation, and the survival rate in the analysis model of the manufacturer was considered in the cost calculation.

Table 3-10 Drug dose settings

Body weight	No. of patients	Proportion of patients	Ravulizumab dose [initial dose] (mg)	Ravulizumab dose [subsequent doses] (mg)	Eculizumab dose [up to Week 2] (mg)	Eculizumab dose [Week 4 onwards] (mg)

≥40 and <60 kg	352	58.18%	2400	3000	600	900
≥60 and <100 kg	249	41.16%	2700	3300		
≥100 kg	4	0.66%	3000	3600		

4. Results of cost-effectiveness assessment

4.1 Revised base case analysis

The results of the re-analysis of the cost-minimization analysis of ravulizumab versus eculizumab are presented in Tables 4-1–4-5. Because all of the analysis results for (a)–(d) showed increased cost of ravulizumab compared with that of eculizumab, the results for (a), which was the easiest to interpret, was regarded as the main analysis results.

(a) Estimation of costs for the 8 weeks of maintenance doses

Comparison of costs (acquisition and management costs) for the 8 weeks of maintenance dose period showed that the cost of ravulizumab was increased by 343,163 JPY as compared with that of eculizumab (Tables 4-1 and 4-2).

Table 4-1 Cost-minimization analysis of ravulizumab versus eculizumab (estimation of costs for the 8 weeks of maintenance doses)

Item	Ravulizumab arm (JPY)	Eculizumab arm (JPY)	Incremental cost (JPY)
Acquisition cost	7,619,419	7,256,592	362,827
Management cost	11,761	31,425	−19,664
Total	7,631,180	7,288,017	343,163

Table 4-2 Calculation process for the cost-minimization analysis (estimation of costs for the 8 weeks of maintenance doses)

Week	Acquisition cost of ravulizumab (JPY)				Management cost of ravulizumab (JPY)	Acquisition cost of eculizumab (JPY)	Management cost of eculizumab (JPY)
	(A) Patient's body weight 40–60 kg [58.18%]	(B) Patient's body weight 60–100 kg [41.16%]	(C) Patient's body weight ≥100 kg [0.66%]	(D) Weighted average of A to C [100%]			
0	7,308,940	8,039,834	8,770,728	7,619,419	11,761	1,814,148	7,856
2	0	0	0	0	0	1,814,148	7,856
4	0	0	0	0	0	1,814,148	7,856
6	0	0	0	0	0	1,814,148	7,856
Total	7,308,940	8,039,834	8,770,728	7,619,419	11,761	7,256,592	31,425

(b) Estimation of costs including the loading dose cost for the lifetime

Comparison of costs (acquisition and management costs) including the loading dose cost for the lifetime showed that the cost of ravulizumab was increased by JPY 106,283,512 as compared with that of eculizumab (Table 4-3).

Table 4-3 Cost-minimization analysis of ravulizumab versus eculizumab (estimation of costs including the loading dose cost for the lifetime)

Item	Ravulizumab arm (JPY)	Eculizumab arm (JPY)	Incremental cost (JPY)
Acquisition cost	2,215,789,123	2,103,806,964	111,982,159
Management cost	3,422,350	9,120,998	−5,698,648
Total	2,219,211,473	2,112,927,962	106,283,512

(c) Estimation of costs including the loading dose cost for the lifetime in consideration of discount rate

Comparison of costs (acquisition and management costs) including the loading dose cost for the lifetime in consideration of discount rate showed that the cost of ravulizumab was increased by JPY 72,451,369 as compared with that of eculizumab (Table 4-4).

Table 4-4 Cost-minimization analysis of ravulizumab versus eculizumab (estimation of costs including the loading dose cost for the lifetime in consideration of discount rate)

Item	Ravulizumab arm (JPY)	Eculizumab arm (JPY)	Incremental cost (JPY)
Acquisition cost	1,476,420,040	1,400,175,873	76,244,167
Management cost	2,281,126	6,073,924	−3,792,798
Total	1,478,701,166	1,406,249,797	72,451,369

(d) Estimation of costs including the loading dose cost for the lifetime in consideration of discount rate and survival rate

Comparison of costs (acquisition and management costs) including the loading dose

cost for the lifetime in consideration of discount and survival rates showed that the cost of ravulizumab was increased by JPY 55,307,436 as compared with that of eculizumab (Table 4-5).

Table 4-5 Cost-minimization analysis of ravulizumab versus eculizumab (estimation of costs including the loading dose cost for the lifetime in consideration of discount and survival rates)

Item	Ravulizumab arm (JPY)	Eculizumab arm (JPY)	Incremental cost (JPY)
Acquisition cost	1,103,856,648	1,045,716,344	58,140,304
Management cost	1,706,071	4,538,938	−2,832,868
Total	1,105,562,719	1,050,255,283	55,307,436

4.2 Revised scenario analysis

The results of the re-analysis of the cost-effectiveness analysis of ravulizumab versus BSC are presented in Tables 4-6–4-8.

Table 4-6 Results of the scenario analysis of the cost-effectiveness analysis

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Ravulizumab	19.86	8.05	855,544,150	819,004,596	101,700,385
BSC	11.81		36,539,554		

Table 4-7 Breakdown of estimated QALY by health state

Health state	Ravulizumab	BSC
Spontaneous remission	3.89	3.09
BTH absent	15.97	0.00
Free C5-related BTH present	0.00	0.00
CAC BTH present	0.01	0.00
History of free C5-related BTH present and BTH absent	0.00	0.00
History of free C5-related BTH present and free C5-related BTH present	0.00	8.72
History of free C5-related BTH present and free CAC BTH present	0.00	0.00
Total	19.86	11.81

Table 4-8 Breakdown of estimated costs by item

Item	Ravulizumab(JPY)	BSC(JPY)	Cost difference(JPY)
Acquisition cost	853,396,454	0	853,396,454
Management cost	1,375,533	0	1,375,533
Treatment cost for BTH	23,084	26,995,823	−26,972,740
Cost of transfusion	728,885	9,543,731	−8,814,846
Cost of vaccines	20,194	0	20,194

Total	855,544,150	36,539,554	819,004,596

4.3 Interpretation of results

The interpretation of the revised analysis by the academic group is summarized as shown in Table 4-9.

Table 4-9 Interpretation of revised analysis results

Population	Paroxysmal nocturnal hemoglobinuria
Comparator	Eculizumab
Reference value for ICER	□ Regular product ■ Product requiring special consideration
Intervals where ICER is most likely to belong	☐ Cost reduction or dominant ☐ 5 million yen or less (7.5 million yen or less) ☐ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) ☐ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) ☐ More than 10 million yen (more than 15 million yen) ■ Efficacy equivalent (or inferior) and expensive
Reason for the decision	Revised analysis using cost-minimization analysis showed that the cost of ravulizumab was increased by JPY 343,163 as compared with that of eculizumab for the 8 weeks of maintenance dose period. Likewise, cost estimations with other conditions also showed increased cost of ravulizumab.
Reference	Although there were analytical issues in the scenario analysis by comparison with BSC, the ICER of ravulizumab versus BSC was estimated to be JPY101,700,385/QALY.

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