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ORIGINAL RESEARCH

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A US cost-minimization model comparing ravulizumab versus eculizumab for the treatment of atypical hemolytic uremic syndrome

Yan Wang[a], Karissa Johnston[b], Evan Popoff[b], Karl-Johan Myren[a], Antoinette Cheung[b], Claudio Faria[a] and Ioannis Tomazos[a]

[a]Health Economics & Outcomes Research, Alexion Pharmaceuticals, Inc, Boston, MA, USA; [b]Broadstreet HEOR, Vancouver, BC, Canada

ABSTRACT

Aims: Ravulizumab, engineered from eculizumab, provides sustained C5 inhibition in atypical hemolytic uremic syndrome (aHUS) while reducing dosing frequency (every 8 vs 2 weeks, respectively). Treatment choice often carries significant financial implications. This study compared the economic consequences of ravulizumab and eculizumab for treating aHUS.

Materials and methods: A cost-minimization model compared direct medical costs for ravulizumab and eculizumab in treating aHUS, assuming equivalent efficacy and safety, and took a US payer perspective, a lifetime horizon, and a 3.0% cost discount rate. The base case modeled adult and pediatric treatment-naïve populations, with characteristics based on clinical trials, and treatment patterns (duration, discontinuation, re-initiation) derived from eculizumab studies with long-term follow-up. Treatment costs (2019 US$) were based on wholesale drug acquisition costs, Centers for Medicare & Medicaid fee schedules, and published disease management studies. Sensitivity analyses were conducted by adjusting relevant variables.

Results: Ravulizumab provided lifetime per-patient cost reductions (discounted) of 32.4% and 35.5% vs eculizumab in adult and pediatric base cases, respectively. Total costs for ravulizumab vs eculizumab were $12,148,748 and $17,979,007, respectively, for adults, and $11,587,832 and $17,959,814, respectively, for children. Pre-discontinuation treatment contributed the largest proportion of total costs for ravulizumab (94.8% and 88.0%) and eculizumab (94.8% and 87.8%) in adults and children, respectively. Across sensitivity analyses, ravulizumab provided cost reductions vs eculizumab.

Limitations: The model included several typical assumptions. Base case patients with more severe stages of chronic kidney disease were assumed not to discontinue treatment, nor to experience an excess mortality risk in either treatment arm, which may not reflect real-world clinical observations. Additionally, rebates and discounts on medication acquisition or administration were not considered.

Conclusions: In US patients with aHUS, ravulizumab provided cost reductions of 32.4–35.5% vs eculizumab, with a reduced dosing frequency for ravulizumab. The magnitude of reductions was consistent across sensitivity analyses.

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare, systemic, and unpredictable disease that can cause severe, progressive organ damage and death in patients of all ages if left untreated[1–4]. Estimates of disease prevalence are variable, and range from 2.2–9.4 cases per million individuals among the general population aged ≥20 years[5]. aHUS is characterized by systemic thrombotic microangiopathy (TMA), resulting from uncontrolled activation of the complement system[3,4,6]. Patients typically experience recurring episodes of hemolytic anemia, thrombocytopenia, and acute kidney injury that ultimately progresses to end-stage renal disease (ESRD)[6], although some patients also develop extra-renal symptoms and organ damage[7].

Eculizumab (Soliris; Alexion Pharmaceuticals, Inc., Boston, MA), a humanized monoclonal antibody administered via intravenous (i.v.) infusion, represents the first complement inhibitor and regulatory-approved treatment for aHUS[8,9], with its efficacy and favorable safety profile demonstrated in four prospective clinical trials[10–13]. Ravulizumab (Ultomiris; Alexion Pharmaceuticals, Inc.) is a humanized monoclonal antibody developed from eculizumab to allow longer-acting C5 complement inhibition while maintaining a favorable safety profile. The safety and efficacy of ravulizumab have been illustrated in a global phase 3 clinical trial in adults with aHUS naïve to complement inhibitors[14]. Ravulizumab was shown to rapidly inhibit and resolve complement-mediated TMA, to be effective at inducing hematologic remission and improving renal function, in addition to demonstrating a

CONTACT Yan Wang yan.wang@alexion.com Alexion Pharmaceuticals Inc, 121 Seaport Blvd, Boston, 02210, MA, USA
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favorable safety profile[14]. Similar observations have been made in an interim analysis of pediatric patients with aHUS who are treatment-experienced or treatment-naive with respect to complement inhibitors[15], as well as in a subgroup analysis of patients with pregnancy-triggered aHUS naïve to complement inhibitor therapy[16]. Further evaluation of ravulizumab has also been completed in pediatric patients naïve to complement inhibitor therapy[17,18]. Ravulizumab has been approved in the US for the treatment of adults and pediatric patients at least 1 month of age with aHUS to inhibit complement-mediated TMA[19], and has also recently been approved in the European Union for patients weighing $\geq$10 kg with aHUS who are complement inhibitor treatment-naïve, or who have received eculizumab for at least 3 months with evidence of response[20]. Importantly, ravulizumab offers a reduced dosing frequency compared with eculizumab (one infusion every 4–8 weeks dependent on patient weight, vs every 2 weeks)[21], reducing the associated patient and healthcare burden[22].

Ravulizumab and eculizumab have been shown to have similar efficacy and safety profiles in populations with paroxysmal nocturnal hemoglobinuria (PNH)[23,24], though it should be noted that the dosing of eculizumab differs in patients weighing >40 kg when used to treat PNH compared with aHUS (900 mg vs 1200 mg every 2 weeks, respectively). In addition, there are no head-to-head studies to indicate any differences in the efficacy and safety of ravulizumab and eculizumab in aHUS, though an indirect comparison of the two treatments has been performed in patients with aHUS[25]. While both offer transformative clinical benefits, the different dosing frequencies of these treatments may have significant financial implications when treating a condition such as aHUS, which has an unpredictable duration and course. The objective of this study was to assess the economic consequences of treatment choice by comparing lifetime per-patient costs (on-treatment, discontinuation, and relapse management) for adult and pediatric patients with aHUS receiving treatment with eculizumab compared with ravulizumab. A cost-minimization model (CMM) was developed, assuming equivalent efficacy and safety profiles for the two treatments, such that cost differences were driven by differences in drug and administration costs and were influenced by the cumulative time spent on therapy. A CMM is an appropriate evaluation method for treatments expected to have the same or similar outcomes, and focuses attention on the cost side of the equation to identify the least costly option[26]. This makes it a suitable model to evaluate the financial implications of treatment choice and guide healthcare decision-making in aHUS.

Methods

Model structure

A CMM was developed to compare lifetime per-patient costs for adult and pediatric patients with aHUS receiving treatment with eculizumab or with ravulizumab. The model was developed using the process recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM)[27] and involved determination of the approach and inputs using clinical study reports, targeted literature reviews, and consultation with clinical and health economic experts to fill any remaining evidence gaps. The model was populated from a US payer perspective regarding direct medical costs. A lifetime horizon was used (up to 100 years of age), representing the duration of a patient's lifespan, and a 3.0% discount rate was applied to costs in accordance with the literature[28–30].

The model structure had three states: on-treatment, discontinue treatment, and relapse (Figure 1(a)). Each state was stratified by four chronic kidney disease (CKD) stages: 0–2, 3a/3b, 4, and 5/ESRD. Mortality could occur in any of these health states, and the model allowed for up to three rounds per patient of discontinuation, relapse, and re-initiation. The decision problem investigated by the model is illustrated in Figure 1(b).

A decision-tree framework was used in the model and followed the same overall structure, as described in Figure 1(a). The model was used to simulate transitions between health states (on-treatment, discontinue treatment, relapse) for base case patients receiving eculizumab or ravulizumab per 2-week cycle, reflecting the recommended dosing schedule of eculizumab, over a lifetime horizon. The decision-tree framework assumed that all transitions happened at the same time for all patients, based on the specified inputs (e.g. time to treatment discontinuation, time from discontinuation to relapse; Figure 2)[31].

The model was similar for both treatments, with the exception of administration schedules and unit costs. The patient population being considered was assumed to comprise two types of patients: complement inhibitor treatment-naïve, referred to as 'newly initiating' patients, and those experienced with eculizumab and continuing treatment with either eculizumab or ravulizumab, referred to as 'treatment-experienced' patients. The latter group were assumed to be established on therapy and would not discontinue from treatment.

To test the impact of the model framework, a Markov model framework was also considered as part of the sensitivity analyses and used to model results for adult and pediatric base case patients (Supplementary Appendix S1, Supplementary Figure S1). The Markov model allowed a distribution of event times by considering that individual patients experience events such as discontinuation, relapse, and treatment re-initiation at different times.

Model inputs

Patient population

The base case analysis simulated transitions for treatment-naïve adult patients. Baseline characteristics (age at model entry, distribution of sex, distribution of CKD stage at model decision point, and proportion of treatment-experienced patients [assumed to be 0%]) were based on adult patients included in a phase 3, open-label, single-arm, multicenter study of ravulizumab (study 311 [ClinicalTrials.gov identifier: NCT02949128][14]). The baseline values used in the base case

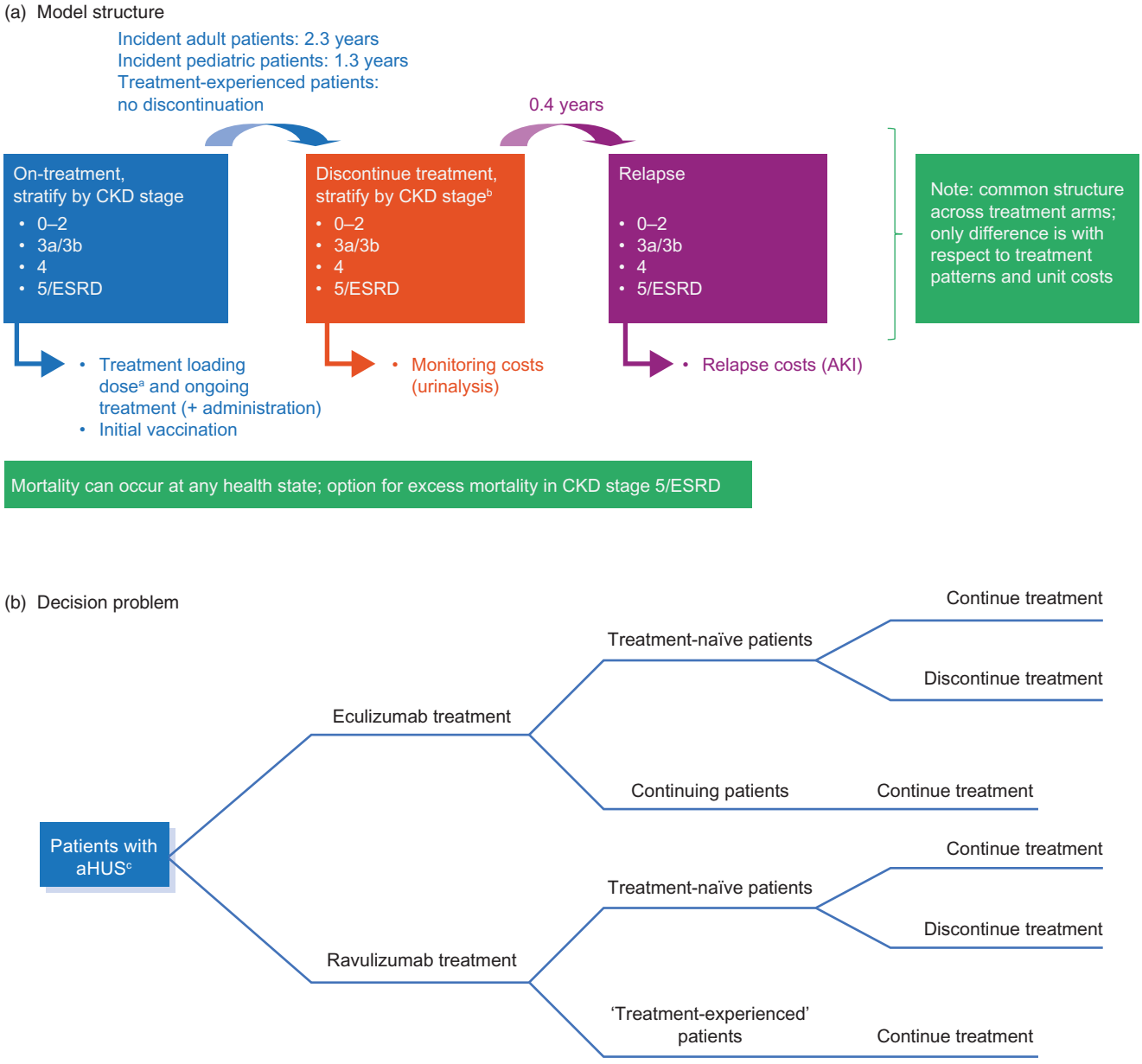

Figure 1. Structure and decision problem of the cost-minimization model. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease. [a]Note that the loading dose for eculizumab is not applied to treatment-experienced patients, who are continuing therapy. [b]Note that discontinuation rates apply to incident patients only because treatment-experienced patients do not discontinue. [c]The decision problem was the same for both adult and pediatric patients. All patients entering the model were treatment-naïve.

analysis are shown in Table 1. A lifetime horizon (i.e. up to 100 years of age) was used in the model. Mortality in the patient population was based on US age- and sex-specific life tables and was used to model the length of time on treatment for patients continuing therapy[32]. Length of time on treatment was also affected by treatment patterns (including percentage of patients discontinuing therapy, and duration of treatment prior to discontinuation), as described below. The base case analysis assumed that no excess mortality risk was associated with CKD Stage 5 or ESRD. This assumption was made based on the evidence currently available for patients with CKD Stage 5 or ESRD in general, as information for such patients as part of an aHUS population is lacking. However, the impact of excess mortality and the proportion of patients with CKD Stage 5 or ESRD were explored as part of the sensitivity analyses performed for this study, as later described.

The model also simulated transitions for a treatment-naïve pediatric population using data from the phase 3, open-label, single-arm, multicenter study (study 312 [ClinicalTrials.gov identifier: NCT03131219][17,33]) of ravulizumab in complement inhibitor treatment-naïve children and adolescents with aHUS (baseline values provided in Table 1). For the pediatric population, the proportion of treatment-experienced patients was also set as 0%. The model took into account the growth and development of pediatric patients as they aged, and the corresponding impact on the weight-based dosing regimens for each treatment.

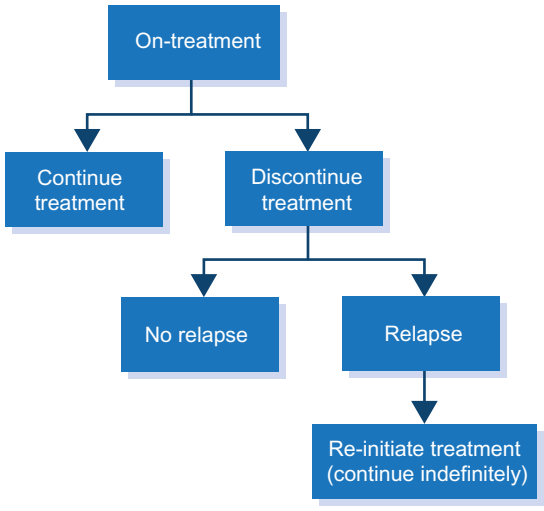

Figure 2. Structure of the decision-tree framework within the cost-minimization model. Abbreviations: CKD, chronic kidney disease. One branch of the tree is shown here, which is applicable to CKD stages 0–2 and 3a–3b. In the decision tree, if a switch (e.g. on-treatment to discontinuation) is assumed to occur for *p*% of patients at time *t* (in years), then the full *p*% of patients will discontinue at time *t* (or the closest 2-week model cycle to time *t*). Different time values can be assessed and compared.

Table 1. Patient characteristics modeled in the base case analyses.

Parameter	Value in adult base case analysis	Value in pediatric base case analysis
Age at start of treatment/model entry, years	42	6
Proportion of female patients, %	66.1	55.6
CKD distribution at model decision point, %		
CKD Stage 0–2	5.5	11.1
CKD Stage 3a–3b	5.5	11.2
CKD Stage 4	16.4	44.4
CKD Stage 5/ESRD	72.7	33.3
Proportion of long-term ("treatment-experienced") patients vs newly initiating, %	0	0

Values may not add exactly to 100% owing to rounding.
Abbreviations. CKD, chronic kidney disease; ESRD, end-stage renal disease.

Treatment patterns

Treatment and discontinuation patterns for newly-initiated patients were expected to vary in each of the different health states. The CMM allowed users to specify the proportion of patients who discontinued, relapsed, and initiated treatment by CKD stage. Doses were applied for the duration of time that patients spent on treatment, with discontinuation and relapse/re-initiation accounted for in the model structure. In the base case analysis, discontinuation rates were set to target an overall discontinuation rate of 45%, based on long-term outcome data for 93 eculizumab-treated patients with aHUS in study C11-003 (NCT01522170)[34]. It was assumed that patients with CKD Stage 4 or 5 at treatment initiation would not discontinue therapy, and so the discontinuation rate in patients with CKD Stage 0–3 was set to match the overall discontinuation rate of 45%. For the base case analysis, this required an assumption that 100% of patients with CKD Stage 0–3 would discontinue. For adult patients who discontinued, the duration of treatment from initiation to discontinuation was assumed to be 2.3 years based on observations from study C11-003, in which adult patients with aHUS treated with eculizumab were found to discontinue at 27.8 months (2.3 years)[34]. Following discontinuation, 50% of all patients were assumed to relapse, with relapse occurring at 4.7 months (0.4 years) from discontinuation[34]. It was assumed that patients reinitiated treatment in the cycle following relapse. For subsequent additional transitions through the health states, the base case of the model assumed that a patient would discontinue treatment only once. In the pediatric base case, the mean duration of treatment was assumed to be 1.3 years (16.1 months) from initiation to discontinuation, based on findings from study C11-003[34]. Time from discontinuation to relapse was assumed to be 0.4 years, as for the adult population[34].

Costs

The CMM included the costs associated with being on-treatment (drugs, administration, and meningococcal vaccination), discontinuation (monitoring), and relapses (acute hospital event and management; Table 2). Post-relapse costs included the cost of restarting treatment with eculizumab or ravulizumab following relapse and the treatment costs from the point of this re-initiation. All costs were estimated in US dollars (US$) for 2019. Discounted (3.0% rate) and undiscounted costs were calculated.

The dosing regimens for eculizumab and ravulizumab, which include both loading and maintenance doses, vary according to patient weight (Supplementary Table S1)[19,35]. Modeling of drug costs was therefore based on patient weight categories to determine the number of vials required for each administration. Different weights per age were considered for patients aged up to 18 years[36,37] and doses calculated accordingly. Adult patients were assumed to stay on an unchanging dose, with loading doses applied at the time of initiation. The cost of administering meningococcal vaccine at time of initiation was also included and was equivalent across treatment arms (US$241.90).

The costs associated with monitoring discontinuation, using urinalysis and microscopy in line with the published literature[4,38–40], and the duration of this monitoring, were equivalent across treatment arms (US$4 per 2-week cycle for the duration of a patient's lifetime; Table 2). The cost of a relapse, which includes associated acute hospital events and therapeutic management, was also assumed to be the same across treatment arms (US$3,882.44 per relapse).

Deterministic sensitivity analyses

Deterministic sensitivity analyses (DSAs) were performed to assess the impact of uncertainty on the modeled results (Supplementary Table S2). Parameters that were adjusted in the DSAs were time horizon, discount rate, excess mortality, age at treatment initiation, and proportion of females. CKD stage, the proportion of treatment-experienced vs treatment-naïve patients, the proportion of discontinuing and relapsing patients, and time to these events were also examined. DSAs

Table 2. Treatment and administration cost inputs.

Input	Value (US$)	Source
Eculizumab		
Eculizumab cost per 300 mg vial	6,523.00	Soliris (eculizumab) Wholesale Acquisition Cost, Micromedex Red Book[49]
Eculizumab i.v. loading dose administration cost, per administration	144.72	CMS, Physician Fee Schedule (PFS), CPT code 96413[50]
Eculizumab i.v. maintenance dose administration cost, per administration	144.72	CMS, PFS, CPT code 96413[50]
Meningococcal vaccine cost	241.90	A 2018 analysis using Optum's de-identified Clinformatics[i] Data Mart Database (2007–2018) and Optum's de-identified Electronic Health Record dataset (2007–2018)[a]. Data are not published.
Discontinuation (monitoring costs of urinalysis and microscopy per 2-week cycle)	4	CMS, Clinical Diagnostic Laboratory Fee Schedule, CPT 81000[41]
Duration of monitoring, years	≤100 years	Assumption
Relapse (acute hospital event + management)	3,882.44	Silver 2017, cost of acute kidney injury (AKI), inflation adjusted[42]
Ravulizumab		
Ravulizumab cost per 300 mg vial	6,404.00	ULTOMIRIS (ravulizumab) Wholesale Acquisition Cost, Micromedex Red Book[49]
Ravulizumab i.v. loading dose administration cost, per administration	176.40	CMS, PFS, CPT code 96413, 96415[50]
Ravulizumab i.v. maintenance dose administration cost, per administration	208.08	CMS, PFS, CPT code 96413, 96415[50]
Meningococcal vaccine cost	241.90	A 2018 analysis using Optum's de-identified Clinformatics Data Mart Database (2007–2018) and Optum's de-identified Electronic Health Record dataset (2007–2018)[a]. Data are not published.
Discontinuation (monitoring costs of urinalysis and microscopy per 2-week cycle)	4	CMS, Clinical Diagnostic Laboratory Fee Schedule, CPT 81000[41]
Duration of monitoring, years	≤100 years	Assumption
Relapse (per event, acute hospital event + management)	3,882.44	Silver 2017, cost of AKI, inflation adjusted[42]

[a]Average procedure cost based on 14 immunization claims in PNH and aHUS patients treated with eculizumab.
Abbreviations. aHUS, atypical hemolytic uremic syndrome; AKI, acute kidney injury; CMS, Centers for Medicare & Medicaid Services; CPT, Current Procedural Terminology; i.v., intravenous; PFS, Physician Fee Schedule; PNH, paroxysmal nocturnal hemoglobinuria.

were also performed for the base case using the Markov model framework.

Two one-way scenario analyses were studied in detail to explore the associated financial implications in both an adult and a pediatric population. One scenario explored the effect of a population composed entirely of treatment-experienced patients, while the other assessed the influence of a fixed 10-year time horizon, as opposed to the lifetime horizon used in the base case.

Results

Base case analyses

Adult patients

In the base case analysis, ravulizumab was associated with lower lifetime per-patient costs than eculizumab in adult patients with aHUS when calculated according to the decision-tree framework.

The total treatment costs for ravulizumab were 32.4% (discounted) and 32.6% (undiscounted) lower than for eculizumab (Table 3a). When costs were discounted, ravulizumab was associated with a cost saving of US$5,830,260 compared with eculizumab (total costs: US$12,148,748 vs US$17,979,007, respectively). The undiscounted total treatment cost of ravulizumab treatment was US$25,224,763 compared with US$37,429,898 for eculizumab: a cost saving of US$12,205,135. Total costs were notably higher (more than double) for the undiscounted analysis vs the discounted analysis (Table 3a), although the relative magnitude of the cost savings remained consistent. The largest proportion of total costs for both therapies was the on-treatment costs (ravulizumab, US$11,515,415 discounted; eculizumab, US$17,042,224 discounted). For both therapies, the combined costs associated with discontinuation, relapse, and post-relapse accounted for only a small proportion of the total cost (5%; Table 4a).

Table 3. Cost-minimization results for ravulizumab versus eculizumab for the base case analyses using the decision-tree framework.

Parameter	Intervention Ravulizumab	Comparator Eculizumab	Intervention versus Comparator
(a) Adult patients			
Discounted			
Total treatment costs (US$)	12,148,748	17,979,007	−5,830,260
Is intervention cost saving?	Yes, 32.4% cost reduction		
Undiscounted			
Total treatment costs (US$)	25,224,763	37,429,898	−12,205,135
Is intervention cost saving?	Yes, 32.6% cost reduction		
(b) Pediatric patients			
Discounted			
Total treatment costs (US$)	11,587,832	17,959,814	−6,371,983
Is intervention cost saving?	Yes, 35.5% cost reduction		
Undiscounted			
Total treatment costs (US$)	36,484,609	55,287,767	−18,803,158
Is intervention cost saving?	Yes, 34.0% cost reduction		

Values may not add exactly, owing to rounding.

For the Markov model framework, results from the adult base case were similar to those seen with the decision-tree framework (Supplementary Appendix S2).

Pediatric patients

Using the decision-tree framework, the total treatment costs for ravulizumab were 35.5% (discounted) and 34.0% (undiscounted) lower than for eculizumab (Table 3b) in pediatric patients aged 18 years or under. Ravulizumab was associated with discounted cost savings of US$6,371,983 compared with eculizumab (total costs: US$11,587,832 vs US$17,959,814, respectively). The undiscounted total treatment cost of ravulizumab was US$36,484,609, compared with US$55,287,767 for eculizumab: a cost saving of US$18,803,158. The magnitude

Table 4. Breakdown of costs for ravulizumab vs eculizumab for the base case analyses using the decision-tree framework.

Parameter	Costs (US$)	
	Ravulizumab	Eculizumab
(a) Adult patients		
Discounted		
Pre-discontinuation treatment costs	11,515,415	17,042,224
Discontinuation monitoring costs	147	147
Relapse costs (AKI)	196	196
Post-relapse treatment costs	632,990	936,441
Total	12,148,748	17,979,007
Undiscounted		
Pre-discontinuation treatment costs	23,837,783	35,374,609
Discontinuation monitoring costs	319	319
Relapse costs (AKI)	212	212
Post-relapse treatment costs	1,386,450	2,054,759
Total	25,224,763	37,429,898
(b) Pediatric patients		
Discounted		
Pre-discontinuation treatment costs	10,192,323	15,772,083
Discontinuation monitoring costs	359	359
Relapse costs (AKI)	412	412
Post-relapse treatment costs	1,394,737	2,186,960
Total	11,587,832	17,959,814
Undiscounted		
Pre-discontinuation treatment costs	31,967,448	48,416,484
Discontinuation monitoring costs	1,078	1,078
Relapse costs (AKI)	433	433
Post-relapse treatment costs	4,515,650	6,869,772
Total	36,484,609	55,287,767

Values may not add exactly, owing to rounding.
Abbreviation. AKI, acute kidney injury.

of costs was notably higher (more than triple) for the undiscounted vs the discounted analysis over a lifetime horizon, and greater than that observed in adults. As previously noted in adult patients, the largest proportion of total costs for both therapies was the on-treatment costs (ravulizumab, US$10,192,323 discounted; eculizumab, US$15,772,083 discounted). The combined costs for discontinuation, relapse and post-relapse accounted for 12% of the total cost (Table 4b).

When considering the Markov model framework, similar results from the pediatric base case were observed as compared with the decision-tree framework (Supplementary Appendix S2).

Deterministic sensitivity analyses

The DSAs demonstrated that ravulizumab remained cost-saving compared with eculizumab in both adult and pediatric patients, regardless of the parameter varied in the base case (Figure 3) or the scenario analyzed.

Adult patients

Using a decision-tree framework, DSA results for base case adult patients were most affected by the time horizon, CKD distribution, and discontinuation patterns (Figure 3(a)), with

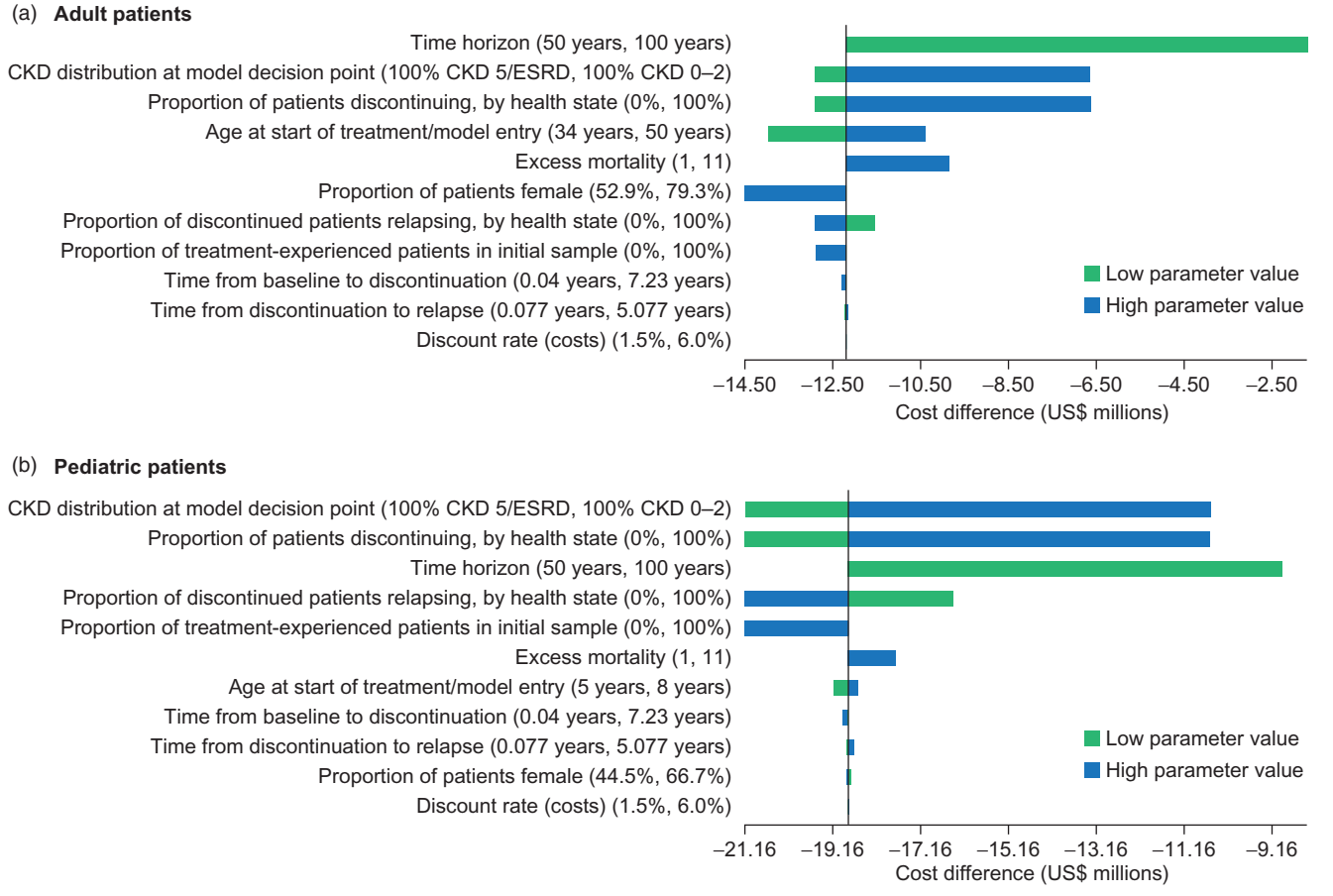

Figure 3. Deterministic sensitivity analysis: influence of parameters on the cost difference (ravulizumab vs eculizumab) for the base case analyses when using the decision-tree framework. Abbreviations. CKD, chronic kidney disease; ESRD, end-stage renal disease.

age at start and the proportion of females also relatively important.

When a population of treatment-experienced adults only was modeled, the total costs for treatment with ravulizumab were 32.3% (discounted) and 32.6% (undiscounted) lower than for eculizumab in the same population (Table 5a). When considering discounted costs, use of ravulizumab provided cost savings of US$6,116,970 compared with eculizumab (total costs: US$12,792,755 vs US$18,909,725, respectively). The undiscounted total treatment cost for ravulizumab was US$26,619,801 vs US$39,480,359 for eculizumab, leading to savings of US$12,860,559. As for the base case, overall costs were more than doubled for the undiscounted vs the discounted analysis (Table 5a), although the magnitude of the cost savings was similar. Because treatment-experienced patients were assumed not to discontinue, and therefore the costs of discontinuation, relapse, and post-relapse treatment were not applicable, these costs represent on-treatment costs only. In this scenario, discount rate was shown to exert the greatest influence on further DSA results, followed by time horizon (Figure 4(a)).

An additional scenario was modeled using a fixed time horizon of 10 years, with all other variables remaining unchanged. Total costs for ravulizumab treatment were 32.9% (discounted) and 32.0% (undiscounted) lower than the cost of treatment with eculizumab in this setting (Table 6a). Ravulizumab provided cost savings of US$1,814,045 compared with eculizumab (total costs: US$3,872,679 vs US$5,686,724, respectively). The undiscounted cost of ravulizumab treatment was US$4,453,158 vs US$6,551,376 for eculizumab, generating savings of US$2,098,218 over the 10-year period. As previously observed in the base case, on-treatment costs accounted for the greatest proportion of total costs (US$3,715,885 and US$5,459,213 for ravulizumab and eculizumab, respectively [discounted]), with costs

Table 5. Cost-minimization results for ravulizumab vs eculizumab in treatment-experienced patients using the decision-tree framework.

Parameter	Intervention Ravulizumab	Comparator Eculizumab	Intervention vs Comparator
(a) Adult patients			
Discounted			
Total treatment costs (US$)	12,792,755	18,909,725	−6,116,970
Is intervention cost-saving?	Yes, 32.3% cost reduction		
Undiscounted			
Total treatment costs (US$)	26,619,801	39,480,359	−12,860,559
Is intervention cost-saving?	Yes, 32.6% cost reduction		
(b) Pediatric patients			
Discounted			
Total treatment costs (US$)	12,997,721	20,155,073	−7,157,352
Is intervention cost-saving?	Yes, 35.5% cost reduction		
Undiscounted			
Total treatment costs (US$)	41,020,115	62,166,074	−21,145,959
Is intervention cost-saving?	Yes, 34.0% cost reduction		

Values may not add exactly, owing to rounding.

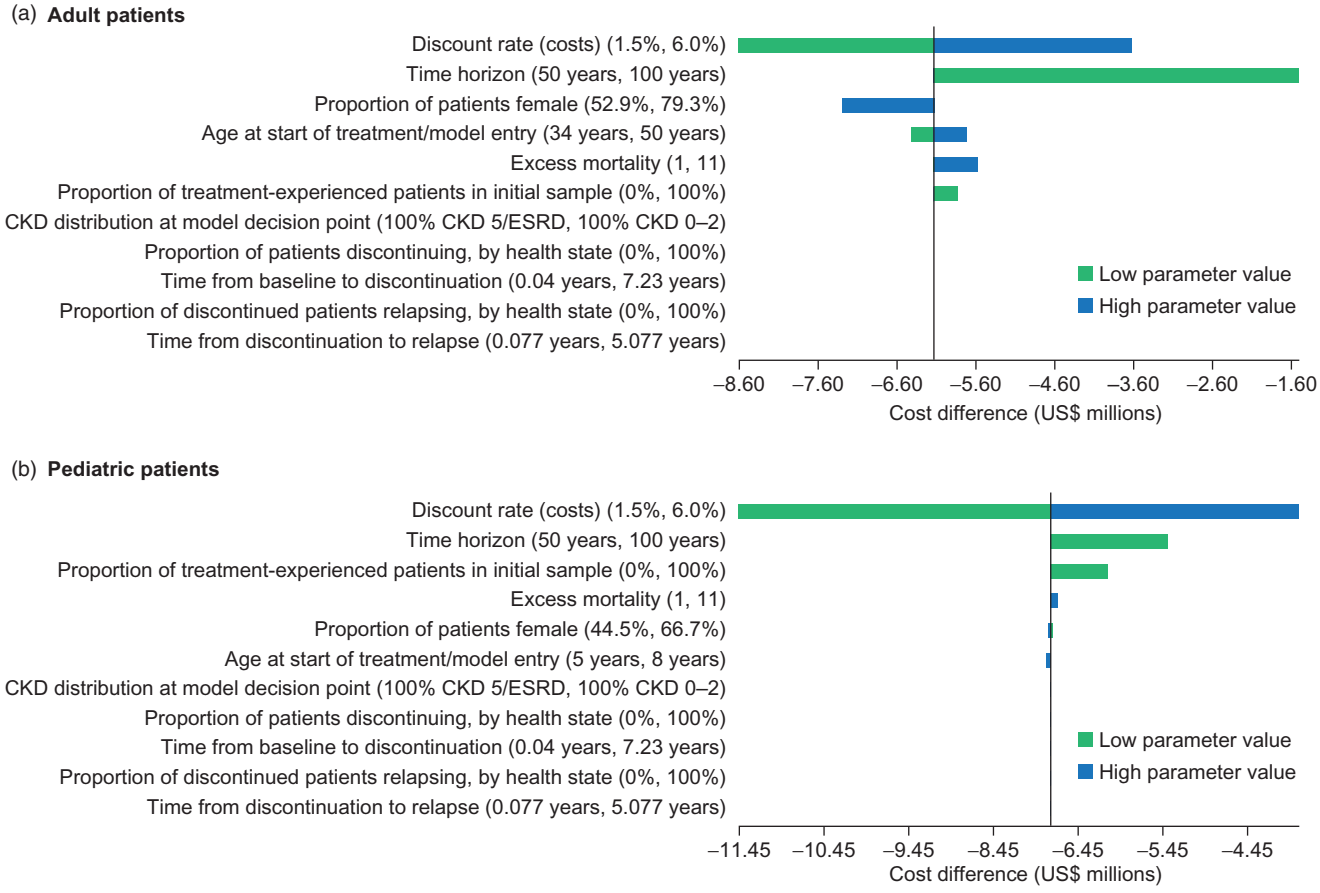

Figure 4. Deterministic sensitivity analysis: influence of parameters on the cost difference (ravulizumab vs eculizumab) in treatment-experienced populations when using the decision-tree framework. Abbreviations. CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table 6. Cost-minimization results for ravulizumab vs eculizumab over a fixed 10-year time horizon using the decision-tree framework.

Parameter	Intervention Ravulizumab	Comparator Eculizumab	Intervention vs. Comparator
(a) Adult patients			
Discounted			
Total treatment costs (US$)	3,872,679	5,686,724	−1,814,045
Is intervention cost-saving?	Yes, 32.9% cost reduction		
Undiscounted			
Total treatment costs (US$)	4,453,158	6,551,376	−2,098,218
Is intervention cost-saving?	Yes, 32.0% cost reduction		
(b) Pediatric patients			
Discounted			
Total treatment costs (US$)	2,411,212	3,816,989	−1,405,777
Is intervention cost-saving?	Yes, 36.8% cost reduction		
Undiscounted			
Total treatment costs (US$)	2,782,082	4,471,684	−1,689,601
Is intervention cost-saving?	Yes, 37.8% cost reduction		

Values may not add exactly, owing to rounding.

Table 7. Breakdown of costs for ravulizumab vs eculizumab over a fixed 10-year time horizon using the decision-tree framework.

Parameter	Costs (US$)	
	Ravulizumab	Eculizumab
(a) Adult patients		
Discounted		
Pre-discontinuation treatment costs	3,715,885	5,459,213
Discontinuation monitoring costs	38	38
Relapse costs (AKI)	196	196
Post-relapse treatment costs	156,560	227,277
Total	3,872,679	5,686,724
Undiscounted		
Pre-discontinuation treatment costs	4,264,767	6,277,797
Discontinuation monitoring costs	46	46
Relapse costs (AKI)	212	212
Post-relapse treatment costs	188,133	273,322
Total	4,453,158	6,551,376
(b) Pediatric patients		
Discounted		
Pre-discontinuation treatment costs	2,167,910	3,404,313
Discontinuation monitoring costs	87	87
Relapse costs (AKI)	412	412
Post-relapse treatment costs	242,804	412,177
Total	2,411,212	3,816,989
Undiscounted		
Pre-discontinuation treatment costs	2,493,938	3,978,287
Discontinuation monitoring costs	101	101
Relapse costs (AKI)	433	433
Post-relapse treatment costs	287,611	492,863
Total	2,782,082	4,471,684

Values may not add exactly, owing to rounding.
Abbreviation. AKI, acute kidney injury.

pertaining to discontinuation, relapse, and treatment re-initiation representing only 4% of overall costs (Table 7a). For this scenario, age at treatment initiation, time horizon, CKD distribution, and the proportion of patients discontinuing treatment exerted the greatest impact on DSA results (Figure 5(a)).

When using the Markov model framework, DSAs were most sensitive to time horizon, discount rate, and excess mortality for the adult base case population (Supplementary Figure S2a).

Pediatric patients

The DSA results for pediatric patients were sensitive to several parameters, some of which were similar to those found in the DSAs for adult patients (Figure 3(b)). DSA results were most sensitive to CKD distribution at model decision point, the proportion of patients discontinuing, time horizon, proportion of discontinued patients relapsing, and proportion of treatment-experienced patients.

When a population of treatment-experienced pediatric patients was modeled, the total treatment costs for ravulizumab were 35.5% (discounted) and 34.0% (undiscounted) lower than for eculizumab (Table 5b). Treatment with ravulizumab was associated with discounted cost savings of US$7,157,352 compared with eculizumab (total costs: US$12,997,721 vs US$20,155,073, respectively). For ravulizumab, undiscounted total treatment costs were US$41,020,115 compared with US$62,166,074 for eculizumab, generating cost savings of US$21,145,959. Costs were over three times higher for the undiscounted vs the discounted analysis over a lifetime horizon and were larger than those seen for adult patients. As for the adult population, these values represent on-treatment costs only, reflecting the assumptions made for treatment-experienced patients in the model. In this setting, DSA results were most affected by discount rate and time horizon (Figure 4(b)).

When modeling a fixed time horizon of 10 years in a pediatric population, total costs for treatment with ravulizumab were 36.8% (discounted) and 37.8% (undiscounted) lower than with eculizumab (Table 6b). Ravulizumab provided cost savings of US$1,405,777 vs eculizumab (total costs: US$2,411,212 as compared with US$3,816,989, respectively). The undiscounted cost of ravulizumab was US$2,782,082 vs US$4,471,684 for eculizumab, resulting in savings of US$1,689,601 over the fixed time horizon. On-treatment costs represented the largest proportion of discounted total costs (US$2,167,910 and US$3,404,313 for ravulizumab and eculizumab, respectively). Discontinuation, relapse, and treatment re-initiation costs made up 11% of the total expenditure (Table 7b). For this scenario and patient population, time horizon, CKD distribution, and proportion of patients discontinuing exerted the greatest impact on DSA results (Figure 5(b)).

For the pediatric base case population, DSA results were most sensitive to variations in time horizon, proportion of discontinued patients relapsing, and excess mortality when using a Markov model framework (Supplementary Figure S2b).

Discussion

This CMM from a US payer perspective evaluated the economic consequences of treatment choice in aHUS by comparing the lifetime per-patient treatment costs for adult and pediatric patients receiving treatment with eculizumab or ravulizumab. In this study, the analysis focused on the journey of a "typical" patient with aHUS, which was anticipated to be accurate at the cohort/population level. While

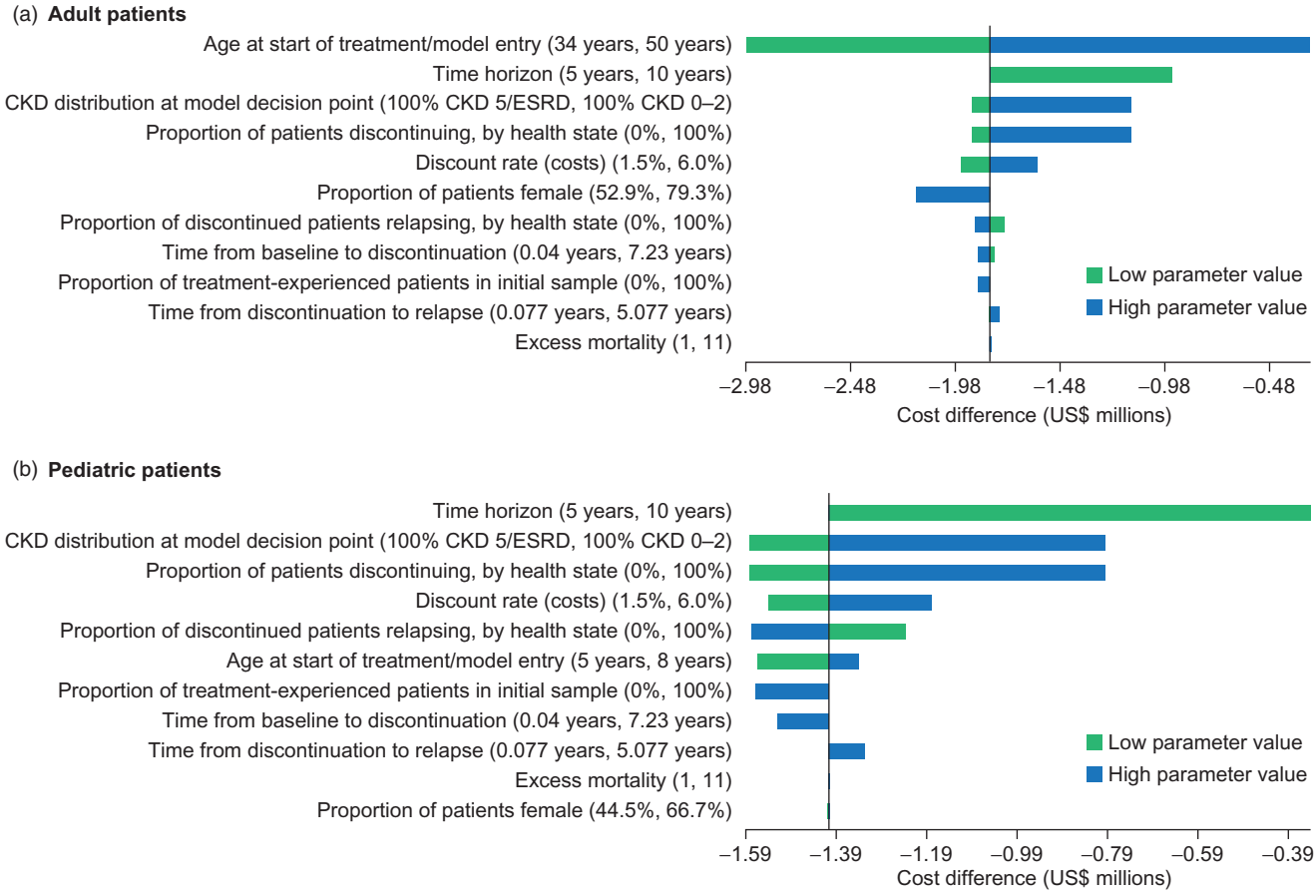

Figure 5. Deterministic sensitivity analysis: influence of parameters on the cost difference (ravulizumab vs eculizumab) for a fixed 10-year time horizon when using the decision-tree framework. Abbreviations. CKD, chronic kidney disease; ESRD, end-stage renal disease.

heterogeneity is expected between individuals, the results produced are reflective of costs averaged across patients. In adult patients (base case), ravulizumab was associated with substantial life-time cost savings of 32–33% relative to eculizumab, corresponding to total savings of US$5.8 million (discounted) or US$12.2 million (undiscounted) when using a decision-tree framework. In children and adolescents, the savings are even greater than in adults, with ravulizumab-related costs 34–36% lower than eculizumab-related costs and total cost savings of US$6.4 million (discounted) or US$18.8 million (undiscounted). The additional expense associated with eculizumab vs ravulizumab treatment was mainly due to the drug cost (part of on-treatment costs) and relapse management costs. In sensitivity analyses, the cost savings with ravulizumab remained robust despite changes in all parameters tested.

As opposed to a more complex cost-effectiveness or cost-utility model, this analysis did not consider disease progression (e.g. changes in CKD stage, or other clinical outcomes such as kidney transplantation or dialysis), and focused primarily on duration of treatment, relapse, re-initiation, and time to mortality. Numerous elements of resource utilization were captured as part of direct costs, including vaccinations, monitoring, and acute hospitalization following relapse[41,42], though we did not incorporate transplantation costs in our comparison. However, as the two therapies were considered clinically equivalent, non-pharmaceutical costs and the need for transplantation were considered the same across treatment arms, and so not including the cost of transplantation would not have affected the observed cost differences. As typical in cost-minimization analyses, a lifetime horizon was selected to allow evaluation of the costs of a long-term condition requiring ongoing medical management, with patient mortality determined using US age- and sex-specific life tables[32]. In pediatric patients, who have a longer time on treatment and lower body weights than adult patients, ravulizumab has the potential to provide even greater overall healthcare cost savings than eculizumab. Indeed, in this study, the cost savings associated with ravulizumab treatment were greater for pediatric patients than for adult patients. Pediatric patients weighing <40 kg require more frequent dosing (every 4 weeks vs every 8 weeks) with lower doses of ravulizumab than adults. The additional costs associated with the increased frequency of infusions in pediatric patients appear to be offset by the lower doses of ravulizumab because total lifetime costs per patient for ravulizumab were almost the same for pediatric and adult patients. In fact, the total discounted costs of ravulizumab treatment in children and adolescents were lower (US$11,587,832 vs US$12,148,748) than in adults. However, the undiscounted costs were almost double for pediatric patients than for adult patients, reflecting the longer length of treatment time for

these patients. As with adults, the additional expense of eculizumab over ravulizumab treatment in pediatric patients was mainly due to the cost of treatment and administration (on-treatment costs). Notably, in adult and pediatric patients, the costs of discontinuation, relapse, and post-relapse treatment contributed 5% and 12% of the overall costs for ravulizumab treatment (US$633,333 and US$1,395,508 discounted), respectively. For both patient populations, post-relapse treatment costs acted as the primary driver of these contributions.

In all scenarios tested in the DSAs, ravulizumab remained cost-saving compared with eculizumab. Even with the most conservative estimates for patient demographics/disease characteristics and discontinuation and relapse parameters, ravulizumab was associated with savings compared with eculizumab. As expected, time horizon had a large impact on absolute cost savings across both frameworks and patient populations, with a fixed time horizon of 10 years resulting in smaller cost savings than 100 years. However, relative savings were similar in both scenarios, with ravulizumab generating discounted cost savings of 32.9% over a 10-year horizon in adult patients vs a reduction of 32.4% over a time horizon of up to 100 years. The corresponding reductions for the pediatric population were a 36.8% and a 35.5% reduction (discounted), respectively. For both adult and pediatric patients, CKD distribution influenced the magnitude of cost savings with the decision-tree framework. Greater proportions of patients with a higher CKD stage led to increased cost savings because these patients were assumed to remain on treatment without any discontinuations and so had a longer treatment duration than otherwise equivalent patients with lower CKD stages.

Additional patient factors were also explored as part of the DSAs. The proportion of treatment-experienced patients was noted to have a small effect on cost savings when using the decision-tree framework, with an increase in savings observed when modeling a population made up entirely of such patients. Modeling a population of treatment-experienced adult patients provided discounted cost savings of US$6,116,970 as compared with savings of US$5,830,260 seen in treatment-naïve base case adults. A similar picture was seen for the pediatric population, with cost savings of US$7,157,352 and US$6,371,983 (discounted) observed for treatment-experienced and -naïve patients, respectively. Because the model assumed that treatment-experienced patients did not discontinue, these individuals would have longer uninterrupted time on treatment than their treatment-naïve counterparts, leading to increased cost savings with use of ravulizumab. The proportion of female patients with aHUS receiving treatment was also noted to exert a greater impact on cost savings among the adult population than in children and adolescents. This was largely attributed to the natural differences in survival between males and females, as well as the generally lower body weight of adult females than adult males. Taken together, the longer survival and lower body weight of females relative to males led to greater time on treatment at lower dose categories, resulting in greater cost savings for ravulizumab vs eculizumab in females.

The approval of eculizumab in 2011 has transformed the treatment of aHUS and changed the prognosis for patients with this rare condition[8,9]. The well-established benefits of this treatment are, however, accompanied by the need for i.v. injections every 2 weeks and the high cost of treatment[43], considering that treatment is recommended to continue over the patient's lifetime. For this study, equivalent efficacy and safety were assumed for eculizumab and ravulizumab, although no direct head-to-head comparison has yet been performed in a population of aHUS patients. Previous data have indicated a strong preference for ravulizumab over eculizumab among patients with PNH, with 93% of patients favoring ravulizumab over eculizumab[44]. This is, at least in part, due to the reduced dosing frequency provided by ravulizumab compared with eculizumab, which may offer financial benefits to healthcare systems and patients, as well as providing reductions in treatment-associated burden and improving overall quality-of-life for patients and caregivers[22]. Notably, the sustained C5 inhibition offered by ravulizumab has also been found to result in less breakthrough hemolysis than with use of eculizumab in patients with PNH, with no breakthrough events occurring owing to free serum C5 with ravulizumab treatment[45]. This improved symptom control may influence patient preference for ravulizumab[45], though it should be noted that eculizumab is administered at a higher dose to patients weighing >40 kg with aHUS than with PNH, which is likely to result in less free C5-related breakthroughs in treated patients with aHUS. In this study, the main driver of cost savings in both adult and pediatric populations was the reduction in on-treatment costs, which accounted for both drug costs and the cost of administering the treatments via i.v. infusion. Therefore, this study supports the hypothesis that the higher dosing frequency of eculizumab vs ravulizumab (26 infusions vs 6–7 infusions a year for patients ≥20 kg) directly accounts for increased healthcare costs.

Few economic evaluations have examined the financial implications of treating aHUS. A cost-effectiveness analysis compared five different treatment strategies, including eculizumab, following renal transplantation in patients with aHUS[46]. Our study compared the economic consequences associated with two complement inhibitors, ravulizumab and eculizumab, for treating aHUS. A CMM was used because, in the absence of head-to-head data, it was assumed that both treatments have similar efficacy and safety profiles and that any cost differences were driven by differences in drug and administration costs. While such studies are limited in patients with aHUS, similar work has been carried out in different populations. Ravulizumab was found to be cost saving in a cost-utility analysis conducted by O'Connell et al.[47], which compared the costs and benefits of both treatments in adults with PNH from a US payer perspective. A semi-Markov model was used for analysis, and lifetime costs and benefit (assessed in quality-adjusted life-years [QALYs]) were discounted at 3.0% per year. Ravulizumab therapy was found to be cost saving compared to eculizumab, providing a saving of $1,673,465 in the base-case analysis, as well as positively impacting patient health-related quality-of-life (QALY gain of 1.67). In the current study, both ravulizumab and

eculizumab are manufactured, and their prices determined, by Alexion Pharmaceuticals. A similar example of this scenario is the cost-utility analysis of ravulizumab and eculizumab conducted in patients with PNH[47]. Regardless of treatment manufacturer, the insights into the financial implications of treatment choice in aHUS provided here remain vital for guiding healthcare decision-making in this field.

There are several assumptions inherent in our model. There are limited data describing discontinuation patterns in patients with aHUS, therefore we made strong assumptions about the likelihood of discontinuing treatment at each CKD stage. Our study assumed that patients with CKD Stage 4 and above at treatment initiation would not discontinue, but that 45% of patients with CKD Stage 0–3 would discontinue (based on rates reported in Menne et al.[34]). In our population, 89% of patients had CKD Stage 4 and above, therefore only 11% of the population were patients with CKD Stage 0–3, who were all assumed to discontinue. Discontinuation rates in our model are therefore lower than those reported in the literature and may not reflect rates in clinical practice. In addition, data regarding risk of relapse were also based on the findings of Menne et al.[34], and the assumptions made regarding treatment discontinuation and relapse patterns may not accurately reflect the treatment patterns seen in clinical practice. In addition, the long-term discontinuation rates reported by Menne et al. could well have been influenced by use of the modified Ham test, though this test is not currently used in clinical practice[48]. With respect to the model, improvements in diagnostics such as the Ham test could allow for better prediction of patient response to therapy, potentially leading to less discontinuation overall (i.e. if some patients who would ultimately discontinue never receive therapy in the first place, owing to better diagnostics). However, we would not anticipate this test to impact the comparison of eculizumab and ravulizumab differentially, and believe ravulizumab would remain a cost-saving therapy overall. The base case assumed that there was no excess mortality risk associated with CKD Stage 5 or ESRD, which also may not reflect real-world clinical outcomes. In addition, the base case did not include rebates or discounts on medication acquisition costs or administration.

Strengths of this analysis include that the model was developed using the process recommended by ISPOR and the SMDM[27]. The modeling approach and parameters were chosen after consultation with clinical and health economic experts, and the inputs were based on data from phase 3 clinical trials[14,17,33,34]. This CMM took a US payer perspective, so caution is needed in extrapolating the results to other countries, but the model may be adapted to other markets by applying country-specific costs, including the unit costs of ravulizumab and eculizumab and differences between populations with regard to demographic characteristics (e.g. differences in age-specific mortality rates). The CMM could also be adapted to reflect different healthcare settings, such as those taking a societal perspective, by incorporating direct non-medical and indirect costs, including cost of time off work to attend treatment sessions and costs incurred by patients and caregivers to attend appointments.

Conclusions

This CMM evaluated the economic consequences of therapy choice in patients with aHUS by comparing the lifetime per-patient costs of ravulizumab and eculizumab treatment in the US. Ravulizumab, which offers an effective treatment for patients with aHUS with a favorable safety profile, was shown to provide substantial cost savings compared with eculizumab. Sensitivity analyses confirmed that the cost savings were maintained and unaffected by changes in various input variables in the model.

Note

i. Optum Clinformatics Data Mart database is a registered trademark of OptumInsight located at Eden Prairie, MN, USA.

Transparency

Declaration of funding

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Declaration of financial/other interests

YW, KJM, CF, and IT are employees of, and may own stock/options in, Alexion Pharmaceuticals, Inc. KJ, EP, and AC are employees of Broadstreet HEOR, a paid consultant of Alexion.

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Author contributions

This study was funded by Alexion Pharmaceuticals, Inc. (study funder). Study design was undertaken by I. Tomazos and Y. Wang (employees of study funder). Study conduct was overseen by I. Tomazos, Y. Wang, K. Johnston, and E. Popoff (employees of study funder and/or contracted by study funder). Data analysis and interpretation was undertaken by I. Tomazos, Y. Wang, K.-J. Myren, C. Faria, K. Johnston, E. Popoff, and A. Cheung (employees of study funder and/or contracted by study funder). All authors discussed and agreed the content, reviewed and provided comprehensive feedback on manuscript drafts, and approved the final version for journal submission.

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Data availability statement

Due to the proprietary nature of this research, the models generated and supporting data are not publicly available.

Previous presentations

An associated abstract was previously submitted to ISPOR-US 2020.

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