SUPPLEMENTARY MATERIAL

Supplementary Table S1. aHUS triggers or associated conditions at ravulizumab initiation.

aHUS triggers or associated conditions, n (%)	**All patients (N = 49)**	**Adult patients (n = 40)**	**Pediatric patients (n = 9)**
No trigger or associated condition	43 (88)	34 (85)	9 (100)
Autoimmune disease	3 (6)	3 (8)	0
Acute infection	1 (2)	1 (3)	0
Drug-induced aHUS	1 (2)	1 (3)	0
Malignancy	1 (2)	1 (3)	0

aHUS, atypical hemolytic uremic syndrome.

Supplementary Table S2. Creatinine and hemoglobin levels before and after ravulizumab initiation and at last follow-up.

Laboratory parameter	Last recorded before or on the date of ravulizumab initiation	First recorded after ravulizumab initiation	Last recorded
Creatinine (µmol/L)			
All patients, n	45	43	48
Median, (IQR)	112.3 (62.8, 158.0)	114.9 (67.0, 165.0)	110.9 (65.9, 165.8)
Adult patients, n	36	35	39
Median, (IQR)	133.8 (89.7, 167.9)	125.0 (88.4, 173.0)	126.4 (88.4, 173.0)
Pediatric patients, n	9	8	9
Median, (IQR)	32.7 (27.4, 46.9)	36.7 (28.3, 55.2)	43.3 (34.5, 53.0)
Hemoglobin (g/L)			
All patients, n	45	41	46
Median, (IQR)	129.0 (116.0, 139.0)	125.0 (115.0, 135.3)	125.3 (115.0, 137.0)
Adult patients, n	36	33	37
Median, (IQR)	130.5 (117.0, 142.5)	125.0 (115.0, 137.0)	125.7 (114.0, 138.6)
Pediatric patients, n	9	8	9
Median, (IQR)	124.0 (115.0, 127.3)	125.0 (113.0, 134.7)	125.0 (119.0, 129.0)

IQR, interquartile range.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3	**Global aHUS Registry Analysis of Patients Switching to Ravulizumab from Eculizumab** The Global aHUS Registry is a multicenter study (NCT01522183) collecting data on adult/pediatric patients with an aHUS diagnosis, regardless of treatment.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4	**Methods** The Global aHUS Registry is a multicenter study (NCT01522183) collecting data on adult/pediatric patients with an aHUS diagnosis, regardless of treatment. Patient characteristics, genetic data, hematological and renal parameters, clinical events (e.g. dialysis, kidney transplantation), and adverse events were extracted from patients who switched to ravulizumab from eculizumab up to July 3, 2023. **Results** Overall, 60 patients switched to ravulizumab (adult: n=43; pediatric: n=17); 11 patients were excluded from effectiveness and genetic analyses (N=49; adult: n=40; pediatric: n=9) because they received <3 months ravulizumab treatment and/or had >1 month between eculizumab discontinuation and ravulizumab initiation. Pathogenic complement variants were identified in 11/49 patients (22%); the most common was a CFH variant (n=5/49 [10%]). During ravulizumab treatment, 20 adverse events occurred in 13 patients, with infection (n=7) the most common. No meningococcal infections or deaths were reported. No new events of dialysis, kidney transplantation, or symptoms of thrombotic microangiopathy were reported. Renal and hematological parameters remained stable after switching to ravulizumab. **Conclusion**

				This was the first real-world cohort analysis of data from patients treated with ravulizumab and reinforces the real-world safety and effectiveness data of ravulizumab in patients with aHUS who switched from eculizumab.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	Cohort-level real-world evidence, such as claims studies and surveys, for ravulizumab in patients with aHUS has only recently emerged,[16, 17] yet the efficacy and safety of ravulizumab in a single large cohort has not been reported beyond clinical trials. In addition, clinical trials did not include adult patients with aHUS who switched to ravulizumab from eculizumab.
Objectives	3	State specific objectives, including any prespecified hypotheses	5	We assessed the real-world clinical characteristics and outcomes of patients with aHUS who switched to ravulizumab from eculizumab using data from the Global aHUS Registry.
Methods				
Study design	4	Present key elements of study design early in the paper	6	The Global aHUS Registry is a multicenter study (ClinicalTrials.gov: NCT01522183) collecting both prospective and retrospective data on demographics, characteristics, natural history, and treatment outcomes in patients with aHUS.[18] The main analysis population for the current study included adult or pediatric patients with aHUS who switched to ravulizumab from eculizumab with at least 3 months of ravulizumab treatment (i.e. sufficient treatment duration to attain at least one maintenance dose) and less than 1 month between eculizumab discontination and ravulizumab initiation, with an initiation date on or after October 1, 2019. The data cut-off for this analysis was July 3, 2023.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	The Global aHUS Registry is a multicenter study (ClinicalTrials.gov: NCT01522183) collecting both prospective and retrospective data on demographics, characteristics, natural history, and treatment outcomes in patients with aHUS.

				'an initiation date on or after October 1, 2019. The data cut-off for this analysis was July 3, 2023.'
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	The main analysis population for the current study included adult or pediatric patients with aHUS who switched to ravulizumab from eculizumab with at least 3 months of ravulizumab treatment (i.e. sufficient treatment duration to attain at least one maintenance dose) and less than 1 month between eculizumab discontination and ravulizumab initiation, with an initiation date on or after October 1, 2019. The data cut-off for this analysis was July 3, 2023.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	–
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7	Both effectiveness and safety outcomes were evaluated. Laboratory parameters included estimated glomerular filtration rate (eGFR; calculated using the Chronic Kidney Disease Epidemiology Collaboration method for adult patients [normal range for adults: > 90 mL/min/1.73 m^2] and the Schwartz method for pediatric patients), platelet count (normal range: 150–450 x 10^6), lactate dehydrogenase (LDH) level, creatinine, and hemoglobin. Assessed clinical events included kidney transplantation, dialysis, and TMA symptoms, measured before and after ravulizumab initiation. The safety analysis included adverse events (AEs), meningococcal infections, and deaths.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7	All data derived from the Global aHUS Registry. Comparability not assessed/relevant
Bias	9	Describe any efforts to address potential sources of bias	N/A	–
Study size	10	Explain how the study size was arrived at	N/A	–

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A	–
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	This was a descriptive study. Continuous data were summarized as median (range). Categorical data were summarized as number and percentage of patients. Laboratory parameters were presented as median (interquartile range).
		(*b*) Describe any methods used to examine subgroups and interactions	N/A	–
		(*c*) Explain how missing data were addressed	N/A	–
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	–
		(*e*) Describe any sensitivity analyses	N/A	–
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7	Overall, data for 60 patients with aHUS who switched to ravulizumab from eculizumab (adult: n = 43, pediatric patients: n = 17) were available in the Global aHUS Registry database. All patients were included in the safety analysis set; following application of inclusion and exclusion criteria, 49 patients were included in the main analysis set (**Table 1**).
		(b) Give reasons for non-participation at each stage	N/A	–
		(c) Consider use of a flow diagram	N/A	Not included.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 18	Table 2 and associated text At ravulizumab initiation, most patients in the main analysis set were adult (n = 40/49 [82%]) and female (n = 36/49 [73%]), with a median age of 35 years (range: 2–72; **Table 2**); 9/49 patients (18%) reported a family history of aHUS. The median (range) time on treatment was 66 (11–155) months for eculizumab and 23 (3–41)

				months for ravulizumab. The most common extra-renal manifestations at any time were gastrointestinal (n = 22/49 [45%]). Most patients (n = 43/49 [88%]) had no identified aHUS trigger or associated condition; the most commonly recorded aHUS trigger or associated condition was "autoimmune disease" (n = 3/49 [6%]) (**Supplementary Table S1**).
		(b) Indicate number of participants with missing data for each variable of interest	N/A	–
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7, 18	The median (range) time on treatment was 66 (11–155) months for eculizumab and 23 (3–41) months for ravulizumab.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8, 9, 21–23	This information is presented in Tables 5 and 6, Figure 1, and Supplementary Table S2.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A	–
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	–
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	Descriptive study.
		(*b*) Report category boundaries when continuous variables were categorized	N/A	–
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	–

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	–
Discussion				
Key results	18	Summarise key results with reference to study objectives	9–11	This Global aHUS Registry study is the first cohort-level analysis to include safety and efficacy data from patients with aHUS treated with ravulizumab and reports the longest real-world treatment exposure and follow-up data to date. Only three AEs were assessed as related to ravulizumab treatment, and no unexpected AEs were reported during ravulizumab treatment, which confirmed the favorable safety profile of ravulizumab demonstrated in clinical trials. Further, both kidney function (as measured by eGFR and creatinine levels) and hematological parameters remained stable after switching to ravulizumab from eculizumab. Importantly, switching to ravulizumab from eculizumab did not necessitate any new events of dialysis or kidney transplantation. Notably, in this study no meningococcal infections were reported during ravulizumab treatment. Overall, no unexpected AEs, meningococcal infections, or deaths were reported during treatment with ravulizumab.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	Limitations of this study include those inherent to registry-derived data, such as missing data and variable lengths of follow-up. Further, the main analysis population did not include patients initiating complement C5 inhibition with ravulizumab only, owing to low numbers at the time of data collection; analysis of these patients is important to comprehensively determine the real-world effectiveness of ravulizumab.

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11	In conclusion, this analysis from the Global aHUS Registry is the first cohort-level analysis of real-world data from adult and pediatric patients with aHUS who switched from eculizumab to ravulizumab, with the longest real-world treatment exposure and follow-up data to date. Overall, no unexpected AEs, meningococcal infections, or deaths were reported during treatment with ravuliuzmab. These data provide further evidence for the safety and effectiveness of ravulizumab treatment in patients with aHUS who switched from eculizumab and reinforce a positive risk–benefit profile of ravulizumab.
Generalisability	21	Discuss the generalisability (external validity) of the study results	9–11	Results discussed in the context of previously published data.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1, 13	The study was funded by Alexion, AstraZeneca Rare Disease, Boston, MA, USA. Medical writing support was provided by Jess Healy, PhD, and Matthew Reynolds, BSc, of Oxford PharmaGenesis Ltd, Oxford, UK, and was funded by Alexion, AstraZeneca Rare Disease, Boston, MA, USA.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.