NICE National Institute for Health and Care Excellence

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Slides for public observers

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Lead team presentation

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Atypical haemolytic uraemic syndrome (aHUS)

- Rare disease causing inflammation of blood vessels and the formation of blood clots, distinct from Escherichia coli (E. coli)-related HUS and thrombotic thrombocytopenic purpura (TTP)
- Associated with genetic or acquired abnormality of proteins in the immune system called complement
- Prevalence estimated to be about 5.5 per million, around 150 to 180 people with the condition are receiving treatment in England
- Poor prognosis without treatment, and people with aHUS experience considerable impact on quality of life
- Can lead to serious damage of vital organs, most commonly the kidneys
- Eculizumab is the current standard of treatment, and is considered effective, requiring infusions every two weeks

Patient and carer perspectives

- Patients are at constant risk of sudden and progressive damage, and failure of vital organs.
- Is a disease of exclusion so can take time for patients to get a confirmed diagnosis.
- Mortality rates range from 10–15% in the acute phase of the disease and within a year of diagnosis, up to 70% of patients progress to end-stage renal failure and need dialysis or die
- Eculizumab is seen as effective but disruptive, with the two-week infusion schedule posing practical issues:

> ***"Life decisions have to be made based on the timing & proximity of treatment"***
> **– aHUS patient**

Source: Patient expert submission

> ***"I mind losing that half days pay every single fortnight… I mind never having been on a two week holiday because I'm scared something will go wrong and I'll be late for my eculizumab [sic]. I mind the stress of trying to arrange even a weekend away because I have to figure out which Friday it will fall on."***
> **– aHUS patient**

Source: KRUK patient organisation submission

Patient and carer perspectives - continued

- USA trial participants found transitioning to ravulizumab straightforward with few adverse events and side effects
- Participants reported the larger gap between infusions as a major advantage of ravulizumab, relieving them of the burden of infusions every two weeks and providing freedom for other activities
- Participants mentioned the longer infusion time as a minor inconvenience.
- Other advantages:
  - Fewer 'traumatic' cannulations / Reduced travel costs / Better for job stability and working hours / Better for family life / Improvement in QoL and beneficial for mental wellbeing

"The positive impact on my mental wellbeing I feel would be the most important. After almost 5 years of living in a "week on, week off" mentality around treatment, I find it can be mentally quite debilitating.

"The 7-week break between treatments would provide a very welcome window of not having to be reminded of… or adapt my life around this disease."

– aHUS patient

Source: Patient expert and KRUK patient organisation submission

Clinical expert perspective

"I think the clinical outcomes will be broadly similar. The outcomes to consider would be quality of life, time off work and education and health care professional time."

- Clinical expert

- Main aim of treatment is to prevent end-stage kidney disease and recurrence.
- Clinically significant treatment response - cessation of haemolysis, normalisation of platelet count and improvement in kidney function.
- There is no clinical unmet need thanks to the availability of eculizumab. No difference in efficacy is expected
- Ravulizumab should be given in the same highly specialised setting as eculizumab

"Ravulizumab would only be used as a second line agent in the majority of cases. Currently eculizumab may be started before all diagnostic tests are available as earlier treatment results in better outcomes. Frequently eculizumab may be stopped after a single dose. With a shorter half-life Eculizumab is a more appropriate agent to use in this situation (i.e. reduced risk of meningococcal sepsis)."

- Clinical expert

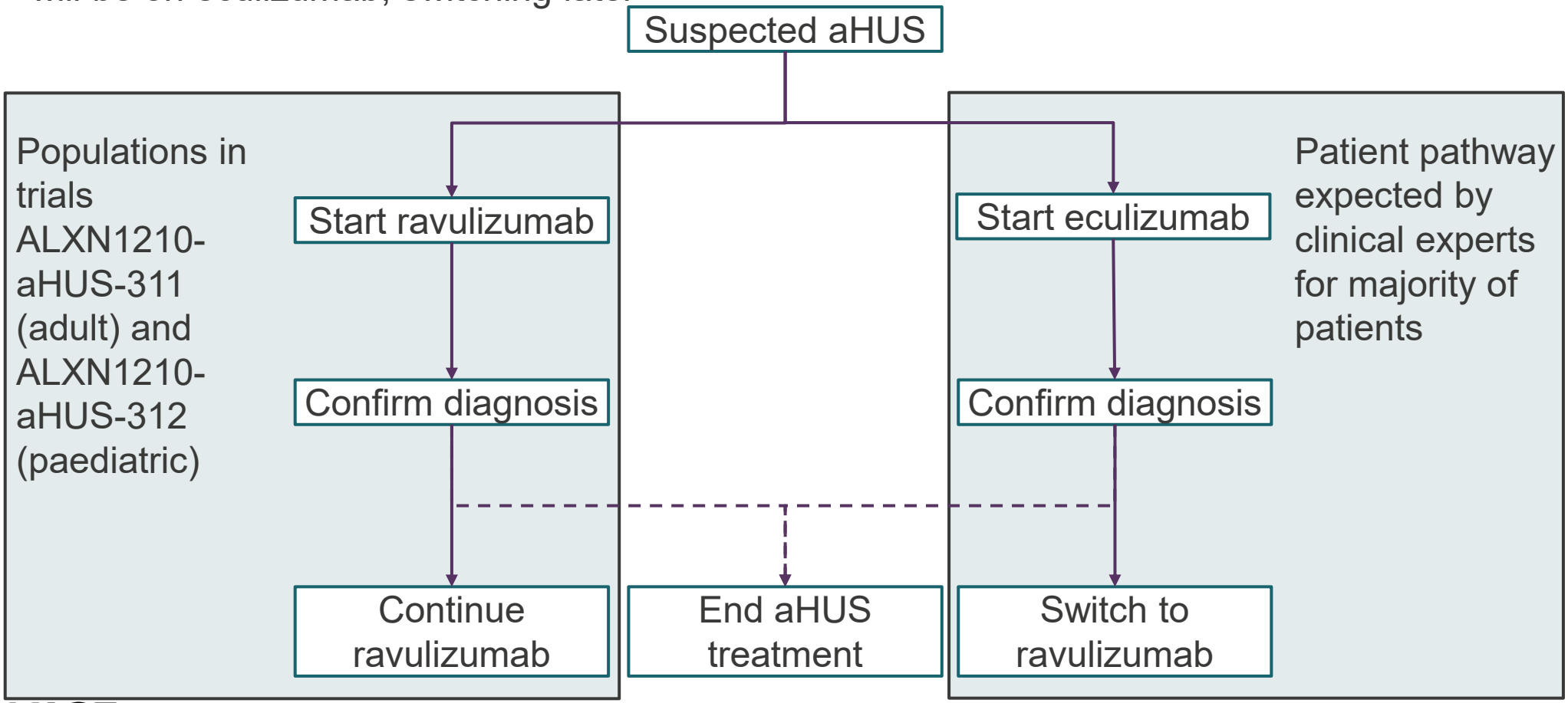
Ravulizumab (Ultomiris, Alexion Pharma UK)

Description of technology	Ravulizumab is a monoclonal antibody that binds to terminal complement protein C5 and prevents the complement activation, therefore blocking blood clots formation and destruction of red blood cells.
Marketing authorisation	Granted marketing authorisation for: “treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab”
Administration	Intravenous infusion
Dosing	Initial loading dose followed by maintenance dosing, starting 2 weeks after the loading dose. Dose quantities vary by body weight. Dosing schedule is every 8 weeks, or every 4 weeks for paediatric patients between 10 and 20 kg
Price	List price: £4,533 for 30 mL vial (10 mg/mL) Average cost per month based on body weight £27,678 Average cost per year: £332,136 Patient Access Scheme is in place and has been updated following technical engagement

Refer to Issue 1

Treatment pathway and positioning of ravulizumab

- Eculizumab (Soliris, Alexion Pharma UK) recommended for aHUS in NICE HST1
- Current pathway involves treatment initiation followed by confirmatory diagnosis by exclusion, at which point treatment can be ended
- Company proposes initiating treatment on ravulizumab, clinical experts anticipate initiation will be on eculizumab, switching later



Background

Ravulizumab trials	Non-comparative trials ALXN1210-aHUS-311 (56 adults) and ALXN1210-aHUS-312 (28 children)
Key results from ravulizumab trials	53.6% adult patients and 77.8% paediatric patients achieve complete TMA response
Comparator in appraisal	Eculizumab
Eculizumab trials	aHUS-C08-002 (16 adults, 1 adolescent); aHUS-C10-003 (22 paediatric patients); aHUS-C10-004 (44 adults). No Asian centres used for these trials
Comparison with eculizumab	Indirect treatment comparison (ITC) analyses. Asian centres removed from ITC after sensitivity analysis
Key result from comparison with eculizumab	No statistically significant/clinically relevant differences
Economic Model	State-transition Markov model, cost-minimisation approach
Company ICER	Dominant, or £[redacted] (negative incremental costs and QALYs)
ERG reported ICER range	Dominant, with range of £[redacted] to £[redacted] in some scenarios ([redacted])

Ravulizumab Trials

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219
Study design	Phase III Single group assignment Open-label Initial Evaluation Period: 26 weeks Extension Period: up to 4.5 years	Phase III Single group assignment Open-label Initial Evaluation Period: 26 weeks Extension Period: up to 4.5 years
Population	Adults with aHUS who are complement inhibitor treatment-naïve	Children and adolescents with aHUS who are (Cohort 1) complement inhibitor treatment-naïve or (Cohort 2) clinically stable following ≥90 days treatment with eculizumab
Number of participants	n=56	Cohort 1 n =18, Cohort 2 n=10, total of 28
Recruitment area	14 countries, [redacted] UK participants, high proportion of Asian participants	8 countries, [redacted] UK participants, high proportion of Asian participants
Intervention(s)	Ravulizumab	Ravulizumab
Comparator(s)	None	None

Source: Company submission, Document B, Tables 4 and 6

Ravulizumab Trial Results: Initial Evaluation Period (FAS)

	ALXN1210-aHUS-311 (n=56)	ALXN1210-aHUS-312 (Cohort 1: n=18) (Cohort 2: n=10)
Complete TMA (cTMA) response n (%)	30 (53.6%)	14 (77.8%) Cohort 1
Time to cTMA response, median days	86.0	[redacted] Cohort 1
CKD Stage improvement n/N*** (%)	32/47 (68.1%)	15/17* (88.2%) Cohort 1; 0/10 Cohort 2
CKD stage worsening n/N*** (%)	2/47 (4.3%)	0/17* (0.0%) Cohort 1; [redacted] Cohort 2
Change in eGFR, median mL/min/1.73m^2 (range)	29 (-13,108)	80 [redacted] Cohort 1; [redacted] Cohort 2
Dialysis discontinuations / number requiring dialysis at initiation	7/29	[redacted] Cohort 1
Dialysis initiations / number not requiring dialysis at initiation	6/27	[redacted] Cohort 1; [redacted] Cohort 2
Participant death	[redacted]**	[redacted]

Source: Adapted from Company submission, Document B, Table 8

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TMA, thrombotic microangiopathy

*[redacted] discontinued because of AE; **[redacted] from septic shock, [redacted] cerebral haemorrhage, [redacted] previously discontinued before death; ***patients with data at baseline and day 407 cut

Ravulizumab Trial Results: Extension Period (FAS)

- Follow-up duration ranged from [redacted] weeks for aHUS-311, [redacted] weeks for aHUS-312 Cohort 1, and [redacted] weeks for aHUS-312 Cohort 2

	ALXN1210-aHUS-311 (n=56)	ALXN1210-aHUS-312 (Cohort 1: n=18) (Cohort 2: n=10)
Complete TMA (cTMA) response n (%)	[redacted]	[redacted] Cohort 1
CKD Stage improvement n/N (%)	[redacted]	[redacted] Cohort 1; [redacted] Cohort 2
CKD stage worsening n/N (%)	[redacted]	[redacted] Cohort 1; [redacted] Cohort 2
Change in eGFR, median mL/min/1.73m^2 (range)	[redacted]	[redacted] Cohort 1; [redacted] Cohort 2
Dialysis discontinuations / number requiring dialysis at initiation	[redacted]	[redacted] Cohort 1
Dialysis initiations / number not requiring dialysis at initiation	[redacted]	[redacted] Cohort 1; [redacted] Cohort 2

Source: Adapted from Company submission, Document B, Table 12

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TMA, thrombotic microangiopathy

Indirect treatment comparison

- Following trials included:
  - aHUS-311 and aHUS-312 representing ravulizumab
  - aHUS-C08-002, aHUS-C10-003, aHUS-C10-004 representing eculizumab
- Numbers of patients used in analysis were:

Molecule	Children (without kidney transplant)	Adults (without kidney transplant)	Adults (with kidney transplant)
Ravulizumab	12	46	7
Eculizumab	20	39	15

- Prognostic score matching undertaken using stabilized weights to reduce baseline differences observed between the ravulizumab and eculizumab trials
- All trial data combined into one dataset and separate analyses undertaken for adult non-transplant, adult transplant, and paediatric patients

Indirect treatment comparison baseline data

- Baseline characteristics considered important were: dialysis status, eGFR, Platelet count, LDH, Systolic blood pressure
- Prior to weighting, baseline data were:

	Rav – adult non-transplant	Ecu – adult	Rav – adult transplant	Ecu – adult	Rav-paediatric	Ecu - paediatric
Dialysis status (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic blood pressure (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Adapted from Company submission, Document B, Tables 17, 18, 19

Key: eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase

Indirect Treatment Comparison Results

- Company concluded no statistically significant differences. ERG referred to significant differences favouring eculizumab (CKD), and others favouring ravulizumab (quality of life)
- The following charts have been created from data used in the ITC post-weighting
- Further outcomes were also compared, not included here

Comparison of key outcomes in adult non-transplant patients for ravulizumab versus eculizumab

Comparison of key outcomes in adult transplant patients for ravulizumab versus eculizumab

Comparison of key outcomes in child patients for ravulizumab versus eculizumab

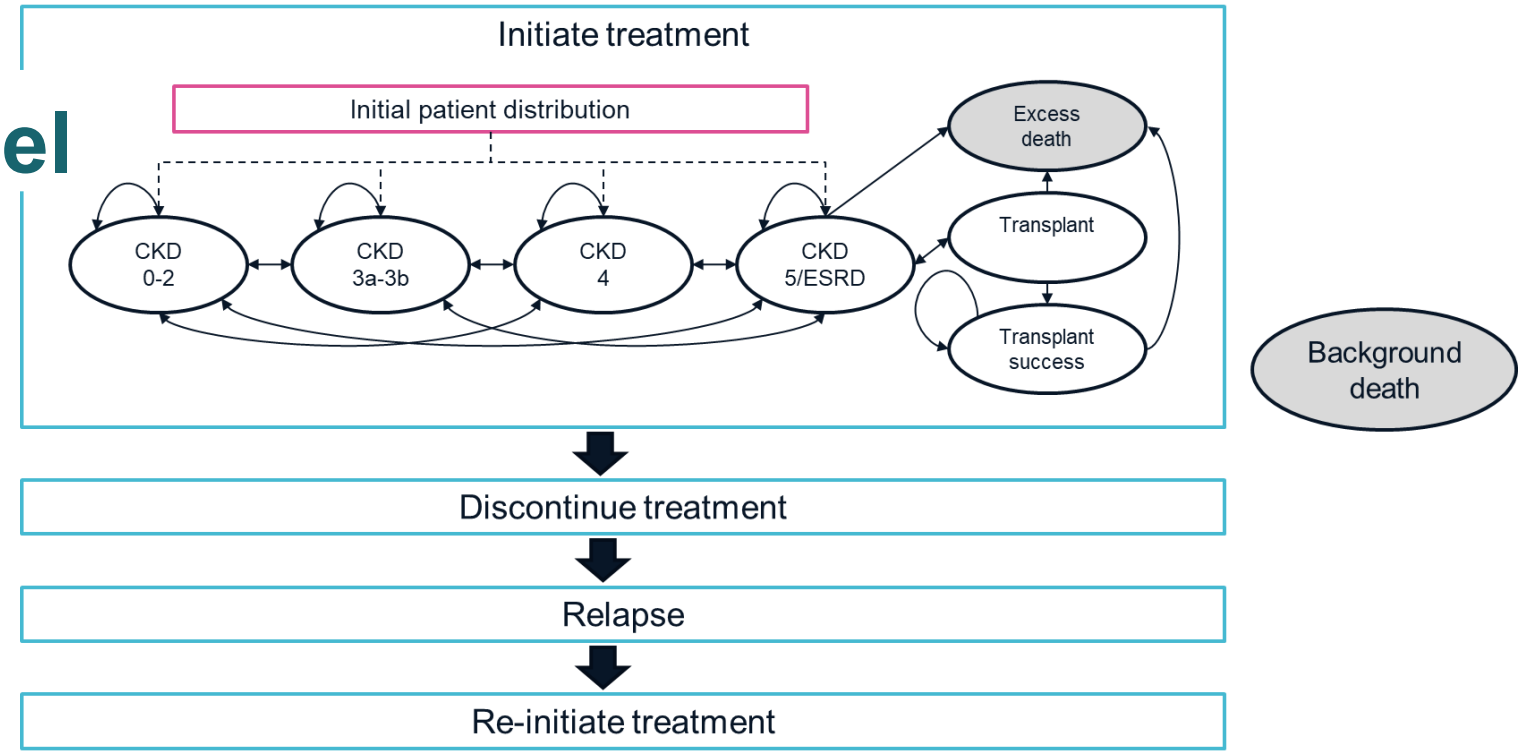
[redacted]

Source: Adapted from Company submission Document B, Tables 21 and 22

Key: CKD, chronic kidney disease; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy

Economic Model

Company presented a cohort state transition model, using separate analyses for data from adult and paediatric patients. Disease states were based on CKD stages, treatment status and relapse.



Company base case:

Parameter	Source
Efficacy	Assumed equivalent with eculizumab, other than 'worst-case' scenario
Utility values	No difference in quality of life between ravulizumab and eculizumab; children and adults assumed to have equal QoL; included [redacted] utility gain due to reduced infusion frequency with ravulizumab (discrete choice experiment)
Discontinuations, adverse events	Discontinuations allowed according to clinical expert opinion; AE rate assumed equivalent with eculizumab
Costs and resource use	Drug costs from company data and MIMS, other costs from scientific literature and NHS reference costs

Key: CKD, chronic kidney disease; ESRD, end-stage renal disease

Sources: Reproduced from Company submission Document B, Figure 16; utility gain from CS p.95

Costs considered in model

Health state	Cost
Drug acquisition	(First year) Ravulizumab: [redacted](adults), [redacted](children); Eculizumab: £352,800 (adults), £168,407 (children)
Administration costs	Ravulizumab: Average £208 per dose; Eculizumab: £195
Meningococcal vaccine	£290
Health state costs (per 2-week cycle)	
Treatment monitoring	£69.70 (first year); £69.57 (after first year)
Dialysis	£1,004.44
Discontinuation cost	£98.87
Relapse cost	£1,272.84
CKD	£16.92 to £22.61, depending on CKD stage
Transplant	£1,059.38
Transplant success	£49.43

- ERG considered that company has taken all relevant costs into account
- Other costs are negligible compared with drug acquisition costs
- Only drug price *'materially impacts'* cost-effectiveness
- For additional costs refer to supplementary slides

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Source: Adapted from ERG report, Table 17
Key: CKD, chronic kidney disease; ESRD, end-stage renal disease

Key issues

Key issues

	Issue	More information	Impact on ICER	Status
1	Generalisability of the ravulizumab trials to NHS practice	Is data from eculizumab-naïve patients representative of clinical practice?		No
2	Relative efficacy of ravulizumab versus eculizumab	Is the assumption of equivalence of ravulizumab with eculizumab justified?		No
3	Long-term efficacy and safety of ravulizumab	Does ravulizumab have long-term safety and efficacy?		No
4	Relapse rate following treatment discontinuation	Is the relapse rate appropriate for patients whose treatment has been withdrawn?		Partially
5	Possibility of providing treatment ‘on demand’ and allowing for multiple treatment discontinuations	Are the company’s assumptions on discontinuations and resumptions of treatment appropriate according to clinical practice?		Partially
6	Treatment discontinuation because of renal response	Is it reasonable to assume ravulizumab treatment would be lifelong or would adequate renal response lead to discontinuation?		Resolved
7	The submission does not consider eculizumab biosimilars	Would future launches of biosimilars affect the patient pathway anticipated by the company?		Resolved

Issue 1: Generalisability of trial results to NHS clinical practice

All patients in ALXN1210-aHUS-311 and two-thirds of patients in ALXN1210-a HUS-312 were complement inhibitor treatment-naïve

ERG:

- Trials included mostly eculizumab-naïve patients. Most patients in UK would initially receive eculizumab treatment, and only after a response/diagnosis confirmed would switch
- Significant differences in baseline characteristics between treatment naïve patients and eculizumab-experienced patients switching to ravulizumab
- Significant proportion of patients in the trials may not have aHUS, e.g. misdiagnosis through different clinical practices in Asia; low complement mutation rate is indicative of misdiagnosis

Company response at TE:

- Trials are generalisable to NHS and reflect both treatment-naïve and eculizumab-responsive
- There are patient groups for whom ravulizumab would be a preferred first-line treatment option
- Identification of complement mutation or autoantibodies not a requirement for diagnosis of aHUS - published analyses suggest only 45-70% of patients show this feature
- Comprehensive body of evidence supporting the safe and effective 'switching' of patients from eculizumab to ravulizumab when the initial and extension phase data of the ravulizumab trials, and data from the ALXN1210-PNH-302 trial that enrolled eculizumab-stable adult patients are all taken into account
- Trial populations may be broader than UK clinical practice, however any resultant bias would not be expected to be in favour of ravulizumab

Issue 1: Trial population not representative of the population seen in UK clinical practice (2)

Clinical experts:

- Most patients will have completed a course of eculizumab
- Adults in the trial had lower rates of mutations (20.5%) vs current data (60-70% in UK patients with confirmed diagnosis of aHUS, aHUS Annual Report). May reflect trial entry with a wide differential diagnosis and patients that would not have been diagnosed with aHUS in UK clinical practice
- One clinical expert considered that the trial broadly reflects clinical practice

ERG views after TE:

- Disagrees with company that the trials are representative of NHS practice and reflect both treatment-naïve and eculizumab-responsive aHUS patients
- Clinical advice to the ERG: ravulizumab only likely to be used where the diagnosis is definitively established, if patients recovered function following first-line eculizumab treatment and long term treatment is considered necessary
- Lower reported mutation rate in the trials compared with that seen in clinical practice suggests many patients without aHUS were enrolled in the studies
- Developments in genetic analysis since the eculizumab trials should result in higher rate of mutations rather than the lower mutation rate observed in the ravulizumab trials
- Extrapolation of PNH trials findings to patients with aHUS is highly uncertain as they are clinically distinct disorders

Issue 1: Trial population not representative of the population seen in UK clinical practice (3)

Other Stakeholders

British Association for Paediatric Nephrology (BAPN) ALXN1210-aHUS-312 trial only

- Cohort 1 - children who were eculizumab-naïve do not represent those who would likely start ravulizumab treatment in the NHS
- Cohort 2 - children who switched from eculizumab to ravulizumab treatment is representative of the cohort of children currently stable on eculizumab treatment in the NHS who would potentially switch to ravulizumab treatment

UK Renal Pharmacy Group (UKRPG)

- Applicable and acceptable – difficult to do head to head comparison as very low patient numbers

aHUS alliance Global Action (AGA)

- Gender and age mixes in the trials could be applicable to UK patients; however Asian and transplant rescue patients are over-represented

Are the results from the trials generalisable to UK clinical practice?

Issue 2: Relative efficacy of ravulizumab versus eculizumab

Issues with trials mean there is insufficient evidence to support the assumption that these treatments have equivalent efficacy and safety

ERG	Company response at TE
Evidence rests on indirect treatment comparison (ITC) of single-arm trials. Prognostic score matching using stabilised weights to reduce baseline differences	Unavoidable uncertainties in ITC, however the biological and clinical evidence, and clinical expert statements, support an assumption of equivalence The 2 drugs share 99% homology; equivalent efficacy and safety are deemed plausible by ERG RCT unfeasible in such a rare condition, data from both aHUS and PNH used in its regulatory filing
Prognostic matching was not carried out for pathogenic mutations despite differences in rates between trials, and expert advice these may affect outcomes	Complement mutations and autoantibodies not highlighted as an important prognostic factor. Genetic testing not mandatory, [redacted]% not tested. Similar TMA response rates were seen in groups with or without mutations
Results showed differences in efficacy could not be ruled out – eculizumab favoured in some important outcomes	Strong belief treatments would be equivalent Difficult to draw conclusions on significance of ITC differences. No apparent trends favouring either treatment. ERG differential efficacy scenario, obtained from one outcome (favouring eculizumab), showed ravulizumab as cost-saving

Issue 2: Relative efficacy of ravulizumab versus eculizumab (2)

Clinical experts:

- With the small numbers enrolled in the study, statistically different outcomes would be very difficult to establish
- Unlikely to be much difference in actual effect on blocking complement haemolytic activity between the drugs

ERG views after TE:

- Disagrees that similar TMA rates support generalisability despite differences in rate of mutations and autoantibodies. Clinical expert has submitted that genetic predisposition does affect disease outcome. New data are insufficient to overcome this limitation
  - One outcome provided (unmatched), conclusions on this outcome (unadjusted for others) are uncertain, small trial size makes untested [redacted]% highly significant
- Disagrees no trends favouring either treatments are observed. Identifies trends favouring eculizumab in clinically important outcomes (e.g. patients requiring dialysis at endpoint)
- Provided scenario analysis assuming differential efficacy in order to account for the possibility the treatments are not equivalent

Other stakeholders: BAPN and AGA

- Both organisations commented that efficacy appeared similar based on the data submitted, however each noted the small trial sizes made it difficult to be sure the drugs are equivalent

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Does ravulizumab have equivalent efficacy to eculizumab?

Issue 3: Long-term efficacy and safety of ravulizumab

There is no follow-up data to inform the long-term safety and efficacy of ravulizumab

ERG:

- Long-term efficacy and safety of ravulizumab are assumed to be equivalent to that for eculizumab
- Biological similarity makes this assumption plausible, but not proven

Company response at TE:

- Data from trials aHUS-311 and aHUS-312 are available up to 52 weeks. Longer-term follow-up data is anticipated but study end date is unpredictable as it depends on commercial availability of the drug in various countries
- Confidential data in PNH shows long-term safety and efficacy up to 5 years
- Post-launch Periodic Safety Update Reports (PSURs) are available for a cumulative 1,529.4 patient years. No new signals or risks were observed in this period
- As long-term data for ravulizumab do not exist, data for eculizumab are used in the model

Clinical experts:

- Requires longer-term follow up and collection of data through a registry such as centralised provision in a national aHUS service
- There is little long-term efficacy and safety data from ravulizumab in atypical HUS

Issue 3: Long-term efficacy and safety of ravulizumab (2)

ERG views after TE:

- Periodic Safety Update Reports (PSURs) show no new signals or risks. Data from PUSRs are not incorporated into the Company's model
- Lack of long-term data remains a source of uncertainty. ERG maintains there is insufficient evidence to assume equivalence of eculizumab and ravulizumab

Other stakeholders:

BAPN

- There are no data available to assess long-term efficacy and safety. Since the data presented cover the period up to July 2019, there may be additional data on the medium term safety and efficacy available in due course

AGA

- Trials show "disappointing" outcomes at 1 year timepoint, suggesting either a lack of efficacy for ravulizumab or a cohort lacking complement-mediated aHUS

Does ravulizumab have long-term safety and efficacy?

Issue 4: Relapse rate following treatment discontinuation

Patients may discontinue treatment, and some proportion relapse. The selection of discontinuation and relapse rates have a significant impact on cost savings observed

ERG:

- Company assumes a constant risk of relapse over time in its submission
- Literature suggests risk of relapse is highest shortly after treatment withdrawal, substantially reducing around a year after withdrawal
- ERG suggests a time-dependent relapse rate be used

Company response at TE:

- Original approach to use a constant relapse rate was a simplifying assumption. Company agrees with ERG, and has incorporated the varying relapse rate into its base case
- Company used scenarios based on UK and global registry data, preferring the UK data as representative of UK practice

Clinical experts:

- Relapse rate following discontinuation will be no different to eculizumab. Likely be determined by the underlying genetic predisposition. As an estimate, individuals with mutations in complement genes will have a 50% relapse rate, and in individuals with no identified complement mutation likely to be close to zero
- This is influenced by underlying disease (and complement genetic or antibody profile) rather than choice of treatment (i.e. ravulizumab vs eculizumab).

Issue 4: Relapse rate following treatment discontinuation (2)

ERG views after TE:

- Reiterated that company's constant relapse rate was flawed. ERG proposed a time-dependant relapse rate based on UK data – ERG did not have access to the global registry
- The approach used by the company is appropriate
- When full registry data are used, results broadly align with those using the UK dataset. However, risk of relapse is generally predicted to be higher for UK patients
- Results of modelling discontinuation and relapse rates are sensitive to the dataset and model fitted. UK dataset appears to predict higher risk of relapse and favours ravulizumab
- ERG prefers to use global dataset because of larger size, longer follow-up time, data not favouring ravulizumab

BAPN

- The constant rate for relapse is inappropriate based on the evidence

AGA

- Only a small minority, much less than 50%, of low risk patients are relapsing after withdrawal
- High risk patients would have a higher relapse rate and possible life-time treatment. More needs to be known about them and their response to different disease triggers
- More answers are also needed on predictors of relapse. Overall, 50% of all patients with aHUS are likely not to need treatment at some stage

Is the time-dependant relapse rate used by the company appropriate?

Issue 5: Possibility of providing treatment 'on demand' and allowing for multiple treatment discontinuations

Company assumes patients who discontinue treatment could re-initiate, but not be allowed to discontinue again

ERG:

- Considers it likely that clinical practice will soon switch to an 'on demand' treatment approach, allowing several discontinuations and re-initiations
- This would drastically alter the costs associated with aHUS treatment, whatever drug is used

Company response at TE:

- 'On demand' treatment allowing for multiple discontinuations is not current UK practice and there are no robust data to support this approach
- The forthcoming SETS study will not resolve this question as it will only examine one discontinuation in treatment

Clinical experts:

- This is possible – with treatment started if initial relapse, an approach currently being studied in SETS-aHUS. However, a strategy of multiple treatment discontinuations (and therefore multiple relapses) unlikely to be tolerated by clinician or patient
- Preliminary data from this suggests that withdrawal of eculizumab from patients may be safely undertaken. Likely that most patients will be able to withdraw from eculizumab with ongoing monitoring. A proportion will relapse requiring longer term treatment

Issue 5: Possibility of providing treatment 'on demand' and allowing for multiple treatment discontinuations (2)

ERG views after TE:

- An important driver of the model is the assumption that patients who discontinue treatment will re-initiate and their subsequent treatment will be lifelong
- ERG has considered the scenario that patients could discontinue several times, but lack of evidence to support this approach renders it uncertain
- The SETS study may support one discontinuation and re-initiation, but the lack of robust evidence means this issue remains unresolved

Other Stakeholders

BAPN

- Option to switch to on-demand treatment, providing subsequent evidence becomes available to support this approach, is likely to be attractive. Anticipates that this will be the likely direction of travel for complement inhibition in aHUS and will require evidence to support the early detection of relapse

AGA

- On-demand when needed reduces potential long-term harm
- Prophylactic treatment ahead of a kidney transplant prevents the harm from rescue therapy. Depending on individual, multiple treatment discontinuations which allow sufficient remission time intervals, are a possibility

Should potential future 'on-demand' treatment be considered?

Issue 6: Treatment discontinuation because of renal response (1)

Company base case did not consider treatment discontinuation because of adequate renal response

ERG:

- Although current guidelines suggest treatment should be lifelong, several arguments in the literature propose withdrawing treatment when adequate renal response has been achieved
- ERG expects this view to be supported by SETS

Company response at TE:

- Original base case model reflected current clinical practice, discontinuation included as a scenario, also allowing for relapse
- In response to TE, company accepted and adopted the ERG approach in its revised base case
- With revised PAS, even if the proportion of time patients spend on treatment following relapse is reduced to [redacted]%, ravulizumab is cost-saving

Issue 6: Treatment discontinuation because of renal response (2)

Clinical experts:

- Proportion of patients with aHUS present too late for treatment with either eculizumab or ravulizumab to be effective - predict that there would be no difference in the level of response
- Likely that ravulizumab will be used second-line where diagnosis is confirmed and response to eculizumab already established. Treatment discontinuation with ravulizumab because of failure to respond is unlikely to be an issue.

Other Stakeholders:

BAPN

- Results from SETS are likely to support discontinuation because of renal response. In this case, even if it has been effective, children (and parents) are likely to want to discontinue treatment when possible

AGA

- Once chronic end stage kidney failure is determined, a remission from aHUS is possible whilst on long term dialysis. Complement inhibitor treatment would usually not be needed, although there may be some residual TMA

Issue 7: The submission does not consider eculizumab biosimilars

Company used eculizumab as its comparator. Eculizumab biosimilars may enter the market after its patent expires

ERG:

- Although eculizumab is currently the only complement-inhibitor treatment option for patients with aHUS, its patent is set to expire in the next 3 years and biosimilar eculizumab treatments are likely to enter the market

Clinical experts:

- The formulation and dosing of a biosimilar is important here. Consideration of eculizumab biosimilar may be important – however, same QoL arguments apply as to eculizumab if the biosimilar is given fortnightly

NICE Technical Team view

- NICE supports the view that future eculizumab biosimilars are not part of the appraisal of ravulizumab

Cost effectiveness results

Company's cost effectiveness results - deterministic

	Incr. costs (£)	Incr. QALYs	ICER Rav vs. Ecu
Original company base-case (original PAS)	[redacted]	[redacted]	Dominates
Post TE - Original company base-case (with revised PAS)	[redacted]	[redacted]	Dominates
Post TE (with revised PAS) - Issue 6 (Renal response included as a reason for treatment discontinuation)	[redacted]	[redacted]	Dominates
Post TE (with revised PAS) - Issue 4 (Time-dependent relapse rates applied following treatment discontinuation) (with revised PAS)	[redacted]	[redacted]	Dominates
Post TE (with revised PAS) - Revised company base-case	[redacted]	[redacted]	Dominates

- Company also provided probabilistic cost savings prior to technical engagement of [redacted]

NICE **Sources:** Company submission, Company TE response

ERG's exploratory analyses with revised PAS- deterministic

Scenario	Discounted costs (£) Rav	Discounted costs (£) Ecu	Discounted QALYs Rav	Discounted QALYs Ecu	Net monetary benefit	ICER Rav vs. Ecu
ERG's preferred base-case • As company's post TE revised base-case **plus** account for Issue 5; potential multiple discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates [redacted]
Issue 2 - ERG differential efficacy analysis (i.e. ITC)						
a) With HRQoL increment for Rav	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Without HRQoL increment for Rav	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: Company's TE response Table 3, page 28; **Key:** wtp, willingness to pay (threshold)

Other Considerations

- Innovation
  - Clinical expert considers ravulizumab to be an incremental improvement over eculizumab
  - Company cites the small improvement as being innovative and having a significant, positive effect for patients (reducing dosing intervals)
- Equality issues
  - No issues raised by company or stakeholders
  - Potential inequality for patients considering parenthood. Pregnancy was among exclusion criteria, and a reason for ending participation in the study. Trial protocol specified:

> ***"Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug"***
>
> **– aHUS-311 protocol**

  - SPC permits use in pregnant women subject to assessment of risks and benefits

Key issues

	Issue	More information	Impact on ICER	Status
1	Generalisability of the ravulizumab trials to NHS practice	Is data from eculizumab-naïve patients representative of clinical practice?		No
2	Relative efficacy of ravulizumab versus eculizumab	Is the assumption of equivalence of ravulizumab with eculizumab justified?		No
3	Long-term efficacy and safety of ravulizumab	Does ravulizumab have long-term safety and efficacy?		No
4	Relapse rate following treatment discontinuation	Is the relapse rate appropriate for patients whose treatment has been withdrawn?		Partially
5	Possibility of providing treatment ‘on demand’ and allowing for multiple treatment discontinuations	Are the company’s assumptions on discontinuations and resumptions of treatment appropriate according to clinical practice?		Partially
6	Treatment discontinuation because of renal response	Is it reasonable to assume ravulizumab treatment would be lifelong or would adequate renal response lead to discontinuation?		Resolved
7	The submission does not consider eculizumab biosimilars	Would future launches of biosimilars affect the patient pathway anticipated by the company?		Resolved