Alexion's Response to the ECD on Use of Eculizumab in the Treatment of aHUS

I. Introduction 2
II. Response to Questions in ECD Section 5.8: The Cost of Eculizumab 3
R&D Costs Only Explain a Portion of the Variance in Price for UODs 4
Variance in Price for UODs is Largely Driven by Differential Value 5
III. Response to Questions in ECD Section 5.11: The Affordability of Eculizumab 5
IV. Response to Questions in ECD Section 5.11: Eculizumab Is Good Value for Money 6
Comparison of Eculizumab in aHUS with Other UODs Currently Funded in England 6
V. Response to ECD Section 5.7: Concerns with NICE's Ad Hoc Budget Impact Model (BIM) 18
VI. Clarification on Select Eculizumab-Specific Clinical Statements 21
Comments to ECD Sections 4.22 and 5.33: Duration of Use 21
Comments to ECD Section 5.4: Current "Stopping Criteria" 22
VII. Comments to the Matters in Paragraph 14 of the Interim Process 22
VIII. Comments on Procedural Matters 23
IX. Conclusion 25

I. Introduction

In the pages that follow, Alexion responds to the Evaluation Consultation Document (ECD) and addresses the questions related to eculizumab as outlined by the Evaluation Committee (the Committee) in the ECD. Also included are responses that clarify some of the clinical statements included in the ECD and matters identified in paragraph 14 of the Interim Process and Methods of the Highly Specialised Technologies Programme (Interim Process). [redacted]

Alexion would like to highlight that it agrees with the majority of the Committee's conclusions, including the strong clinical statements made that emphasize eculizumab is an extremely effective treatment option for patients with aHUS, as follows:

- "Eculizumab is an effective treatment for patients with atypical haemoloytic uraemic syndrome (aHUS) and represents a significant development in the management of a serious condition" (ECD, p. 3);
- "…In all of the studies, treatment with eculizumab led to substantial decreases in thrombotic microangiopathy activity, and an improvement in kidney function and quality of life in most patients. The Committee heard from the clinical specialists that, since they began prescribing eculizumab, the benefits seen in their patients have been greater than they had originally anticipated. They remarked that many patients were able to stop dialysis after starting treatment with eculizumab, and that non-renal benefits, such as improvements in gastrointestinal symptoms, were also seen" (ECD, p. 18);
- "The Committee heard from the clinical specialists that the underlying complement disorder is essentially reversed with eculizumab treatment and that there is emerging evidence that benefits are sustained over time" (ECD, p.19); and
- "The Committee accepted that eculizumab is a step change in the treatment of patients with aHUS and could be considered a significant innovation for a disease with a high unmet clinical need" (ECD, p.23).

In addition, Alexion agrees with the Committee's conclusion that despite the differences in the Economic Review Group's (ERG's) economic model[1] and Alexion's model, "both analyses produced substantial QALY gains of a magnitude that is rarely seen for any new drug treatment" (ECD p. 29). Moreover, the Committee acknowledges that Alexion's economic model is conservative and likely underestimates the health gains associated with eculizumab for patients with aHUS (ECD, p. 23), points for which we strongly agree.

In Sections 5.8 and 5.11 of the ECD, the Committee stated that there were two issues that impeded it from recommending the use of eculizumab in aHUS:

- Section 5.8: The Committee "concluded that it had not been presented with sufficient justification for the high cost per patient of eculizumab in light of the manufacturing, research and development costs of a medicinal product for the treatment of a very rare condition"; and
- Section 5.11: The Committee "noted that, while there is no specific budget for the provision of highly specialised services in the NHS in England, the resources available for commissioning

[1] As stated in our previous review and comment documents regarding the ERG model, we reiterate that the ERG model is seriously flawed as it assumes no excess likelihood of death associated with end-stage renal disease (ESRD); patients in that model spend 30 or more years in ESRD, which has little to no bearing with clinical reality and is therefore seriously flawed.

such services are not unlimited and therefore it remained uncertain on whether the results of the cost consequence analysis demonstrated good value for money."

Furthermore, in Section 5.7 of the ECD, NICE includes an ad hoc budget impact estimate based on assumptions Alexion believes are faulty and not aligned with the commercial realities currently experienced in England. Our responses to the questions raised by the Committee in these three sections follow.

II. Response to Questions in ECD Section 5.8: The Cost of Eculizumab

In Section 5.8 of the ECD, the Committee requests the following information from Alexion:

- "*whether there were any clinical or safety requirements during clinical development that might justify the development cost of eculizumab being materially greater than for other treatments for small populations;*
- *the post marketing research plans and their costs, for eculizumab for the treatment of aHUS and for other indications;*
- *an explanation of the relationship between the development cost of eculizumab and the price being proposed for the NHS; and*
- *any additional information that the company considers will help the Committee reach a conclusion on whether the incremental therapeutic improvement of standard therapy justifies the proposed cost of eculizumab*".

Alexion assumes that the Committee's request stems from paragraph 41 of the Interim Process and Methods of the Highly Specialised Technologies Programme (the Interim Process) that states "*the Committee will also take into account what could be considered a reasonable cost for the medicine in the context of recouping the manufacturing, research and development costs from sales to a limited number of patients*"; however, we are concerned that the Committee's questions extend beyond NICE's remit.

Specifically, Alexion understands that NICE's remit in relation to HSTs <u>does not involve pricing</u>, but instead is to provide advice to the NHS on whether a particular technology should be made available for the treatment of NHS patients, and if so, under which circumstances. The applicable regulatory framework supports our view as follows:

- The price for a medicinal product is determined either in accordance with the Health Service Branded Medicines (Control of Prices and Supply of Information) (No. 2) Regulations 2008 or with the provisions of the Pharmaceutical Price Regulation Scheme 2014, rather than by NICE;
- NICE's procedures do not state at any point that the Committee will conduct a formal analysis of the price for an HST or any other technology or explain how information, such as that requested by the Committee, will be assessed to determine whether a price is "justified"; and
- NICE's Guide to the Methods of Technology Appraisal (The Methods Guide) indicates in terms "*The Committee is not able to make recommendations on the pricing of technologies to the NHS*". (While the Methods Guide refers to technology appraisals rather than HST evaluations, the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013, describe NICE's functions in relation to the two procedures in similar terms.)

Based on the above, Alexion strongly believes that the questions as posed in Section 5.8 of the ECD fall outside NICE's remit as they appear to require justification for the price of eculizumab in the context of costs associated with the development of the product, including future research plans for additional (potential) indications. It is unclear to Alexion how such information is relevant to the specific decision required of the Committee, which is whether eculizumab should be commissioned for patients suffering from aHUS. Consideration of such information by the Committee, in our view, would be suspect in terms of an appropriate process for NICE decision making as well as any subsequent review of that decision. Furthermore, the Committee's request fails to recognize the complexities of any assessment of

development costs, including the costs incurred in relation to the development of compounds that ultimately failed and were never marketed. It also fails to provide a definition of the costs that should be taken into account, both in relation to eculizumab and any other products currently funded by the NHS (which would require to be reviewed for comparison purposes to some extent, even though they are indicated for different diseases and their manufacturers are not participating in the current evaluation). Moreover, it provides no indication as to how such costs will be considered in the current evaluation. A procedure in which the Committee would conduct an undefined and novel assessment based on undisclosed criteria and methods is fundamentally unfair and, in the context of uncertain parameters and inconsistencies in the availability of data for different products, will inevitably produce conclusions that are arbitrary and unreasonable.

Despite these concerns, and following discussions with NICE staff both on March 20, 2014 and April 24, 2014, Alexion acknowledges the Committee's general interest in understanding the variation in price between treatments for very small patient populations and treatments for more traditional patient populations, and seeks to be responsive to the Committee's request. Therefore, we provide the Committee with background information about the role of research and development (R&D) costs for UODs, which is intended to assist the Committee in understanding why products for any rare condition are costly. It is important for the Committee to note, however, that R&D costs only explain a small portion of the variance in price between UODs and more traditional therapies, and comparisons of R&D costs between manufacturers is challenging. Instead, the Committee should focus on the main driver of price variation between UODs and traditional products, which is the differential product value combined with the limited size of the treated population. These points are described in more detail below.

R&D Costs Only Explain a Portion of the Variance in Price for UODs

As the Committee is no doubt aware, the very small size of the eligible ultra-rare disease patient population is in itself a relevant factor to be considered against a backdrop where substantial manufacturing and R&D costs must be recovered. These costs need to be considered in conjunction with the high level of financial risk assumed by all companies that invest in the discovery and development of products without any assurances of approval. That said, there are unique challenges associated with the development of ultra-orphan therapies that are often not as heavily present when conducting research on products for more traditional patient populations. Specifically, despite the very small number of patients studied, sponsors must often open and operate multitudes of clinical trial sites in order to recruit (diagnose, qualify, and treat) study participants. As a result, companies must at times incur costs for opening sites that may or may not ultimately produce patients or results relevant to the review and approval of the product being studied.

Furthermore, the cost of products that treat ultra-rare diseases must not only reflect the substantial development costs invested, but must also reflect the cost of research candidate failures associated with discovering treatments for ultra-rare diseases. Research failures are intrinsically more likely in ultra-rare diseases because such diseases typically do not have established regulatory pathways, minimal science is available to align with potential endpoints, mechanisms of action of therapeutic candidates may more likely be novel without demonstrated alignment to the science, and the small numbers of patients makes dose-finding more challenging. Additionally, the cost must reflect future research efforts, the substantial costs associated with biologics manufacturing (as opposed to small molecule manufacturing), ongoing quality assurance efforts, critical efforts to educate clinicians on the ultra-rare diseases being treated, and on-going efforts in support of patient education, awareness, and access. Although some of these efforts are not necessarily unique to the discovery and development efforts of sponsors for ultra-rare disease therapies, again, the extremely small size of the ultra-rare disease patient population being treated locally, as well as globally, provides significant insight into the marketed costs of ultra-rare products compared to more traditional ones.

With regard to Alexion's ongoing mission and investment in the R&D of transformative therapies for patients suffering from life-threatening, rare and ultra-rare diseases, it is important to note that we incur substantial expenses globally associated with patient registries and other studies and efforts designed to not only augment our clinical understanding of such conditions, but also to meet additional regulatory

requirements. We also have a robust pipeline of therapies under development we hope will eventually come to market and provide hope to other patients suffering from ultra-rare diseases that are currently bereft of treatment options. In England alone, we have directly invested £[redacted][2] in support of patients through funding of clinical trials, eculizumab development, medical marketing and physician education, which combined have contributed directly to England's standing as a leader in the treatment of both paroxysmal nocturnal haemoglobinuria (PNH) and aHUS. Further, we have invested £501 million[3] in total costs globally to bring eculizumab to market in 2007 and an additional £448 million[4] of continued R&D for eculizumab for PNH, aHUS, and other severe and ultra-rare diseases since 2007. Notably, Alexion continues to fund several aHUS patients in England through our clinical trial programs; we additionally fund a highly effective and patient-friendly home-care program for patients with both PNH and aHUS, in cooperation with leading clinicians in order to maximize treatment compliance and minimize travel demands on very ill patients as well as consumption of hospital/NHS resources. We also sponsor Ph.D. programs for students in England interested in pursuing careers in rare disease research, and continue to expand our presence in and contribution to England's economy through job growth and investment in the medical system.

In addition, Alexion believes it is important for the Committee also to understand that the current price of eculizumab in England is among the lowest in the world, and is the lowest price in Europe. While we provide critical analysis in the pages that follow highlighting the relatively lower cost and higher value of eculizumab as compared to other rare and ultra-rare disease products funded by the NHS, we feel strongly that the fact that England already benefits from the lowest price in Europe, and one of the lowest globally, is relevant context for consideration as the overall costs of treating aHUS patients in England is effectively subsidized by payers and patients outside of England.

Variance in Price for UODs is Largely Driven by Differential Value

As noted above, while the cost of R&D and manufacturing are important variables in helping to explain the variation in cost between products for ultra-rare versus more traditional diseases, the most important determinant of price difference between rare/ultra-rare disease treatments is the value a product is expected to generate for patients and society. This concept is almost uniformly accepted by international healthcare purchasers and this principle is at the heart of the NICE system, including the Interim Process for evaluation of HSTs. Therefore, the Committee should focus its review on the analysis Alexion has provided in Section IV below comparing the value offered by eculizumab in aHUS relative to its cost when compared with other UODs currently funded in England.

III. Response to Questions in ECD Section 5.11: The Affordability of Eculizumab

In Section 5.11 of the ECD, the Committee has requested information from the NHS regarding the "affordability" of eculizumab for aHUS. In Alexion's view, any remaining questions with regard to affordability should not preclude a positive recommendation for eculizumab for the following reasons:

1) The NHS is already funding eculizumab for the treatment of aHUS and has been doing so since September 2013 when it adopted the treatment recommendations proposed by the Clinical Priorities Access Group (CPAG) in July 2013, consistent with the clear clinical priority placed on treating aHUS patients. In circumstances where the NHS has also already prioritized aHUS funding, it is curious that the Committee would raise concerns regarding product affordability, particularly at such a late point in the process.
2) NICE's estimates with regard to the inputs used for its ad hoc BIM are based on several faulty assumptions that are explained in detail below. As such, we believe the overall costs associated

[2] Investment has been approximately $[redacted] USD, which is £[redacted] GBP using the exchange rate of 1 USD to 0.59 GBP on May 5, 2014.
[3] Investment has been approximately $850 million USD, which is £501 million GBP using the exchange rate of 1 USD to 0.59 GBP on May 5, 2014.
[4] Investment has been approximately $760 million USD, which is £448 million GBP using the exchange rate of 1 USD to 0.59 GBP on May 5, 2014.

with eculizumab to the NHS will be less and, therefore, affordable in any event, given the high clinical value received. Furthermore, despite claims to the contrary in the ECD, Alexion provided directly to the Committee, in our September 2013 submission, the information requested relating both to a cost-consequence model as well as a thorough BIM. Although we specified that this information must be held as commercial-in-confidence, which we are entitled to do, detailed and sufficient information relating to cost, value, market uptake, and the expected overall budget impact, was provided to the Committee to enable a final decision on eculizumab to be made. To claim otherwise contravenes existing facts.

3) Systemic concerns over the broad affordability of drug therapies approved prior to December 31, 2013, including eculizumab, currently lack reason and are in doubt given the 2014 Pharmaceutical Price Regulation Scheme (PPRS) agreement reached between the Department of Health (DH) and the Association of the British Pharmaceutical Industry (ABPI) in November 2013. Specifically, the DH and the ABPI jointly and publicly stated that the newly adopted PPRS, to which Alexion is a voluntary participant, was designed to "provide Government with surety on the level of NHS expenditure on all branded medicines supplied by companies in the voluntary scheme." As a direct result, PPRS-members (including Alexion) have agreed to jointly rebate overspend by the NHS by way of PPRS payments, beginning this year, meaning that overall NHS drug spending on branded drugs within the scheme, and specifically noting that eculizumab would be in this scheme, will be fixed with certainty at a pre-determined level. Although Alexion recognises that individual medicinal products funded by the NHS should still provide value for money (and we provide detailed information to the Committee to satisfy this requirement for eculizumab in aHUS), overall affordability considerations should be of significantly less concern to the NHS, particularly in circumstances where, as in this case, there is a very high clinical need and in the context of an effective treatment.

Given the above, any objection to the national commissioning of eculizumab for aHUS based specifically on affordability grounds would appear to be contrary to Government commitment to support innovative new treatments, and inconsistent with the DH's arrangements for controlling the medicines budget. Furthermore, as outlined in detail below, eculizumab represents clear value when compared to other UODs currently funded by the NHS.

IV. Response to Questions in ECD Section 5.11: Eculizumab Is Good Value for Money

As described above, UODs are not commercially feasible at prices comparable with treatments for more populous diseases, and the relationship between rarity and price has been observed empirically.[5] Therefore, when considering the cost and value derived from a UOD such as eculizumab in aHUS, the appropriate benchmark for cost relative to benefit are other UODs currently available to patients under the NHS. The Committee evidently agrees, since it has requested information from NICE concerning "a set of cost reference points for highly specialised treatments compared with other treatments commissioned through specialised services" (ECD, pg. 24).

Comparison of Eculizumab in aHUS with Other UODs Currently Funded in England

Recognizing that eculizumab for aHUS is the first HST to be evaluated under the new NICE process, Alexion seeks to assist the Committee by providing comparative data between the price of eculizumab and other UODs, along with supporting data about the products' effectiveness, measured by quality adjusted life years (QALYs). Specifically, Alexion has undertaken a comparison of the added value and annual cost of eculizumab versus a cohort of 11 comparable UOD products that are currently funded by the NHS in England and Wales (Table 1). The sample was selected using the following criteria:

- Pharmaceutical treatments for severe chronic and congenital disorders that are comparable to aHUS;

[5] Drummond, Michael F., et al. "Assessing the economic challenges posed by orphan drugs." International journal of technology assessment in health care 23.01 (2007): 36-42.

- Ultra-orphan drugs (UODs) for diseases with a prevalence less than 1 in 100,000 patients (according to the Orphanet website at www.orpha.net); and
- Treatments that are currently funded by the NHS in England.

Collectively, the evidence shows that eculizumab for aHUS is not the most costly product when compared to UODs that are currently accessible through the NHS, yet it is the product associated with the greatest QALY gain by a substantial margin.

Table 1. Sample of UODs and Commissioning Status in England and Wales

Product Molecular Name	Product Brand Name	Indication*	Commissioning Status in England and Wales	Source
Galsulfase	Naglazyme® 1mg/ml	Mucopolysaccharidosis VI	Funded by NHS England	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013
Idursulfase	Elaprase® 2mg/ml	Mucopolysaccharidosis II	Funded by NHS England	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013
C1-inhibitor (human)	Cinryze® 500U	Acute attacks in Hereditary angioedema	Funded by NHS England	(a) NHS England 2014 (d) NHS England 2013 (e) AWMSG 2013
Ivacaftor	Kalydeco® 150mg	Cystic fibrosis in patients ≥6 yrs who have G551D	Funded by NHS England	(a) NHS England 2014 (f) NHS Commissioning Board 2013
Eculizumab	Soliris® 300mg	aHUS & Paroxysmal Nocturnal Haemoglobinuria (PNH)	TBD (for aHUS)	Not yet applicable for aHUS
velaglucerase alfa	Vpriv® 400U	Type I and type II Gaucher's Disease	Funded by NHS England Recommended by SMC	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013
Laronidase	Aldurazyme® 100IU/ml	Mucopolysaccharidosis I	Funded by NHS England/ Recommended by AWMSG	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013 (g) AWMSG 2005
alglucosidase alfa	Myozyme® 50mg	Pompe disease	Funded by NHS England/ Recommended by AWMSG	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013 (h) AWMSG 2006
Imiglucerase	Cerezyme® 400U	Type I and type II Gaucher's Disease	Funded by NHS England	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013
agalsidase beta	Fabrazyme® 35 mg	Fabry disease	Funded by NHS England/ Recommended by AWMSG	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013 (i) AWMSG 2006
agalsidase alfa	Replagal® 1mg/ml	Fabry disease	Funded by NHS England/ Recommended by AWMSG	(a) NHS England 2014 (b) AGNSS 2012 (c) NHS England 2013 (j) AWMSG 2007

Notes and Sources:
Drug names gathered from Orphanet (www.orpha.net).
*Indication listed as per "indications for NHS England Drug List" 17 December 2013.

(a) NHS England. Medicines not published through national prices set in the National Tariff published on 17 December 2013 and directly commissioned by NHS England (Excel Spreadsheet). 2014. Available at: www.england.nhs.uk/wp-content/uploads/2014/03/drugs-list-v8.xlsx
(b) AGNSS Annual Report 2011/12 (Table 11). 2012. Available at: http://www.specialisedservices.nhs.uk/library/21/AGNSS_Annual_Report_20011_12.pdf.
(c) NHS England. 2013/14 NHS Standard Contract for Lysosomal Storage Disorders Service (Children). 2013. Available at: http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf.
(d) NHS England. Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema. 2013. Available at: http://www.england.nhs.uk/wp-content/uploads/2013/04/b09-p-b.pdf.
(e) AWMSG. Final Appraisal Recommendation No: 0313: C1 inhibitor (Cinryze®) 500 units powder and solvent for solution for injection. 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/73.
(f) NHS Commissioning Board. Clinical Commissioning Policy: Ivacaftor for cystic fibrosis (G551D gene). 2013. Available at: http://www.england.nhs.uk/wp-content/uploads/2013/09/a01-p-a.pdf.
(g) AWMSG. Advice Reference No.180. 2005. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/180.
(h) AWMSG. Advice Reference No.17. 2006. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/17.
(i) AWMSG. Advice Reference No.12. 2006. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/12.
(j) AWMSG. Advice Reference No.11. 2007. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/11.

Table 2 provides the dosing schedule for each of the drugs in Table 1, and their Pharmacy Purchasing Price (PPP) per dose or per pack as available in the British National Formulary (available at www.medicinescomplete.com). The average weight of a child used was 15kg, and the average weight of an adult was 75kg.

Table 2. Dosing Schedule and Price per Dose for UOD Products Funded in England

Product (Molecular/ Brand Name)	Patient Type	Recommended dosage for treatment*	Content of container	Calculated dosage for average weight	Number of vials or packs needed for average weight pt	PPP* per vial (for injectables) and per pack (for tablets) (Without VAT)
Galsulfase (Naglazyme)	Adult	1 mg/kg body weight administered once every week	5 ml vial (contains 5 mg galsulfase)	75 mg per week	15	£982.00
Galsulfase (Naglazyme)	Child	Same as for adults	Same as for adults	20 mg per week	3	£982.00
Idursulfase (Elaprase)	Adult	0.5 mg/kg body weight every week	3 ml vial (contains 6 mg of idursulfase)	37.5 mg per week	6.25	£1,985.00
Idursulfase (Elaprase)	Child	Same as for adults	Same as for adults	10 mg per week	1.25	£1,985.00
C1-inhibitor (Cinryze)	Adult	1000 units every 3 or 4 days is the recommended starting dose for routine prevention against angioedema attacks; the dosing interval may need to be adjusted according to individual response. After reconstitution, one vial contains 500 units of C1 inhibitor (human) per 5 ml (corresponding to a concentration of 100 units/ml)	5 ml vial (represents 500 UI)	1000 Units every 4 days	2	£668.00
C1-inhibitor (Cinryze)	Child	Same as for adults	Same as for adults	1000 Units every 4 days	2	£668.00
Ivacaftor (Kalydeco)	Adult	Adult and child over 6 years, 150 mg every 12 hours	Pack of 56 tablets	300 mg per day	2 tables a day	£14,000.00
Ivacaftor (Kalydeco)	Child	Same as for adults	Same as for adults	200 mg per day	2 tablets per day	£14,000.00

Product (Molecular/ Brand Name)	Patient Type	Recommended dosage for treatment*	Content of container	Calculated dosage for average weight	Number of vials or packs needed for average weight pt	PPP* per vial (for injectables) and per pack (for tablets) (Without VAT)
Eculizumab (Soliris)	Adult	aHUS dosing regimen: Initial phase: 900 mg every week for the first 4 weeks. Maintenance phase: 1200 mg for the 5th week, followed by 1200 mg every 14 ± 2 days.	30 ml vial (contains 300 mg of eculizumab)	900 mg for 4 weeks + 1200 mg on week 5 then 1200 mg every 2 weeks	Initial Phase: total 12 vials Maintenance Phase: total 96 vials	£3,150.00
Eculizumab (Soliris)	Child	aHUS dosing regimen (10 to <20 kg) Initial phase: 600 mg for first week Maintenance phase: 300 mg at week 2; then 300 mg every 2 weeks	Same as for adults	600 mg weekly x 1; 300 mg at week 2; then 300 mg every 2 weeks	Initial Phase: total 2 vials Maintenance Phase: total 26 vials	£3,150.00
Velaglucerase alfa (Vpriv)	Adult	60 units/kg administered every other week	20 ml vials (contains 400 IU)	4500 Units every 2 weeks	11.25	£1,410.20
Velaglucerase alfa (Vpriv)	Child	Same as for adults	Same as for adults	1200 Units every 2 weeks	2.25	£1,410.20
Laronidase (Aldurazyme)	Adult	100 units/kg body weight administered once every week.	5 ml concentrate for solution in a vial (represents 500 IU)	7'500 Units per week	15	£444.70
Laronidase (Aldurazyme)	Child	Same as for adults	Same as for adults	2000 Units per week	3	£444.70
Alglucosidase alfa (Myozyme)	Adult	20 mg/kg of body weight administered once every 2 weeks	10 ml vial (contains 50 mg of alglucosidase alfa)	1500mg every 2 weeks	30	£356.06
Alglucosidase alfa (Myozyme)	Child	Same as for adults	Same as for adults	400 mg every 2 weeks	6	£356.06
Imiglucerase (Cerezyme)	Adult	60 units/kg every 2 weeks. After reconstitution, the solution contains 40 units (approximately 1.0 mg) of imiglucerase per ml (400 U/10 ml).	20 ml vials (represents 800 IU)	4500 Units every 2 weeks	5.6	£1,071.29

Product (Molecular/ Brand Name)	Patient Type	Recommended dosage for treatment*	Content of container	Calculated dosage for average weight	Number of vials or packs needed for average weight pt	PPP* per vial (for injectables) and per pack (for tablets) (Without VAT)
Imiglucerase (Cerezyme)	Child	Same as for adults	Same as for adults	1200 Units every 2 weeks	1.1	£1,071.29
Agalsidase beta (Fabrazyme)	Adult	1 mg/kg body weight administered once every 2 weeks. After reconstitution one vial contains 35 mg of agalsidase beta per 7 ml (corresponding to a concentration of 5 mg/ml)	7 ml vial (contains 35 mg of agalsidase beta)	75 mg every 2 weeks	2.14	£2,196.59
Agalsidase beta (Fabrazyme)	Child	Same as for adults for children 8-16 years. No dosage regimen is recommended for children 0-7 years (safety and efficacy not established for these patients).	Same as for adults	20 mg every 2 weeks	0.428	£2,196.59
Agalsidase alfa (Replagal)	Adult	0.2 mg/kg body weight every other week. Each vial of 3.5 ml of concentrate contains 3.5 mg of agalsidase alfa	3,5 ml vial (contains 3.5mg of agalsidase alfa)	15 mg every 2 weeks	4.28	£1,068.64
Agalsidase alfa (Replagal)	Child	Same as for adults for children 7-18 years of age	Same as for adults	4 mg every 2 weeks	0.856	£1,068.64

*PPP = Pharmacy Purchasing Price.

Table 3 estimates the annual cost of each of the UODs included in the sample. In situations where the drug is indicated for both children and adults, separate costs have been calculated for each patient type. As noted above, annual costs were estimated using the list prices available in the British National Formulary (available at www.medicinescomplete.com) and dosing schedules used are those described in each drug's SmPC. As in Table 2, the average weight of a child used was 15kg and 75kg for adults.

Table 3. Annual Costs for UOD Products of Relevance in England

Product (Molecular/Brand Name)	Adult - 75 kg Annual Cost of Treatment/patient	Children - 15 kg Annual Cost of Treatment/ patient
Galsulfase (Naglazyme)	£768,062	£153,610
Idursulfase (Elaprase)	£646,897	£129,378
C1-inhibitor human (Cinryze)*	£121,910	£121,910
Ivacaftor (Kalydeco)	£182,500	£182,500
Eculizumab (Soliris)	£340,198	£88,199
Velaglucerase alfa (Vpriv)	£416,549	£82,720
Laronidase (Aldurazyme)	£347,819	£69,564
Alglucosidase alfa (Myozyme) (Juvenile)	£278,490	£55,698
Imiglucerase (Cerezyme)	£156,408	£30,723
Agalsidase beta (Fabrazyme)	£122,554	£24,511
Agalsidase alfa (Replagal)	£119,246	£23,849

*Cinryze is recommended by the AWMSG for the acute (i.e. treatment and pre-procedure prevention) and routine prevention of angioedema attacks. In England, Cinryze is recommended for treatment in acute attacks in hereditary angioedema; long term regular prophylaxis requires prior approval by an Individual Funding Requestor Group Prior Approval from commissioners where there is a clinical indication for its use (NHS Commissioning Board; April 2013. Reference: NHSCB/B09/P/b). Costs in our comparison assume Cinryze for chronic use (long term regular prophylaxis) based on its approved labelling by the AWMSG.

The number of discounted incremental QALYs provided by each UOD was used as an objective measure of added clinical benefit for the purposes of this comparison. Table 4 provides estimates of discounted QALY gains for each product from two perspectives:

- that of the manufacturer (for example data provided by the manufacturer to an health technology assessment (HTA) authority, or a publication sponsored by the manufacturer); and
- that of an independent HTA agency (e.g., NICE ERG group or independent academic authors).

Table 4. Incremental QALY Gain for UOD Sample as Estimated by Independent Sources and by the Product's Manufacturer

Product (Molecular/Brand Name)	Incremental QALY gain*		Sources
	Manufacturer Estimate	ERG / Independent HTA Estimate	
Galsulfase (Naglazyme)	No Data Identified (NDI)	NDI	N/A
Idursulfase (Elaprase)	5.96	NDI	(a) AWMSG 2007
C1-inhibitor human (Cinryze)	4.57**	NDI	(b) AWMSG 2013
Ivacaftor (Kalydeco)	5.26	2.16	(c) Whiting 2014
Eculizumab (Soliris)	25.22***	10.14***	(d) NICE 2014 (for aHUS)

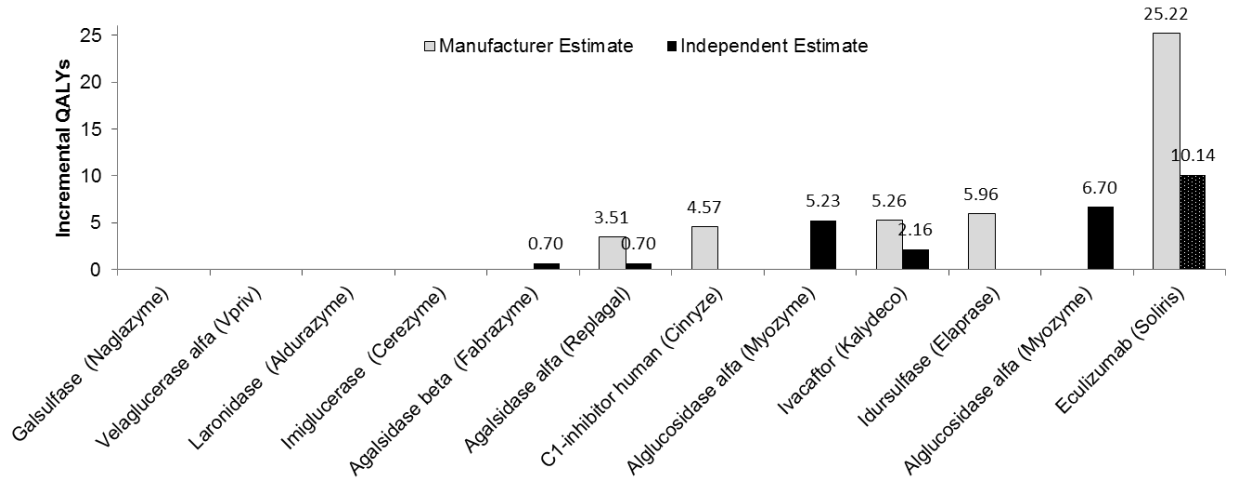
Product (Molecular/Brand Name)	Incremental QALY gain*		Sources
	Manufacturer Estimate	ERG / Independent HTA Estimate	
Velaglucerase alfa (Vpriv)	NDI	NDI	N/A
Laronidase (Aldurazyme)	NDI	NDI	N/A
Alglucosidase alfa (Myozyme) juvenile	NDI	6.7	(e) Kanters 2013
Alglucosidase alfa (Myozyme) juvenile	NDI	5.23	(f) Castro 2012
Imiglucerase (Cerezyme)	NDI	NDI	N/A
Agalsidase beta (Fabrazyme)	NDI	0.7	(g) Rombach 2013
Agalsidase alfa (Replagal)	3.51	0.7	(h) AWMSG 2007 (g) Rombach 2013

Notes:
No Data Identified (NDI) means no publicly available data have been identified.
*Discounted unless stated otherwise.
**Costs in the comparison assume Cinryze for chronic use (long term regular prophylaxis) based on its approved labelling by the AWMSG. Therefore, QALYs in our analysis come from the AWMSG Appraisal Report for Cinryze, in which Cinryze is compared to another branded UOD product (Berinert®). Cinryze assumes therapeutic equivalence in their base case, or an incremental QALY gain of "0". Cinryze is associated with an absolute (not incremental) 4.57 QALYs in the base case, which we report as an absolute maximum QALY gain for this product.
***This ERG's 10.14 QALY gain was based on a flawed model that did not include excess mortality for patients in ESRD. The ECD states that the 25.55 QALY gain for eculizumab calculated by Alexion's model is likely a conservative estimate.
Sources:
(a) AWMSG. Final Appraisal Report: Idursulfase (Elaprase) Advice No: 1207. 2007. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/162.
(b) AWMSG. AWMSG Secretariat Assessment Report. C1inhibitor (Cinryze) Reference No.73. 2013 Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/73.
(c) Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technol Assess 2014;18(18). The intermediate scenario in Whiting et al. is used for the "ERG / Independent HTA Estimate" input; the optimistic scenario is used for the "Manufacturer Estimate" input. Note that the conservative estimate in Whiting et al. is 1.27.
(d) NICE. Evaluation consultation document. Eculizumab for the treatment of atypical haemolytic uraemic syndrome. 2014. Available at http://www.nice.org.uk/guidance/highlyspecialisedtechnologyevaluations/atypicalhaemolyticuraemicsyndrome/EvaluationConsultationDocument.jsp.
(e) Kanters TA, Plug I, Rutten-van Mölken MPMH, Redekop W et al. Cost-effectiveness of enzyme replacement therapy (ERT) with alglucosidase alfa in classic-infantile patients with pompe disease. Value in Health 2013; 16(7):A384. Also available at: http://www.bmg.eur.nl/english/imta/ispor/cost_effectiveness_of_enzyme_replacement_therapy_ert_with_alglucosidase_alfa_in_classic_infantile_patients_with_pompe_disease/.
(f) Castro H. The cost-effectiveness of enzyme replacement therapy (ERT) for the infantile form of Pompe disease: comparing a high-income country's approach (England) to that of a middle- income one (Colombia) Rev. salud pública. 14 (1): 143-155, 2012
(g) Rombach S, Hollak C, Linthorst G, et al. Cost-effectiveness of enzyme replacement therapy for Fabry disease. Orphanet Journal of Rare Diseases 2013; 8:29. Available at: http://www.ojrd.com/content/8/1/29.
(h) AWMSG. Final Appraisal Report: Agalsidase alfa (Replagal) Advice No: 1107. 2007 Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/11.

Note that for the independent HTA agency review of eculizumab QALY figure, we use the ERG's estimate of QALYs of 10.14 even though this estimate was calculated using a flawed model. Most notably, as we have documented in previous responses to NICE and the ERG, the ERG did not include in its model excess mortality for patients in ESRD, allowing patients to pool in ESRD for more than 30 years, which is not clinically or practically feasible. Regardless of the flaws in the ERG's model, the Committee still notes in the ECD that the 25.55 QALY gain estimated in the Alexion model is likely a "conservative" estimate (ECD page 23).

Figure 1 depicts the incremental QALY gain estimates from independent and manufacturer sources for the sample of UODs. Incremental QALYs were not found for all drugs in this sample; specifically, publicly available data were not identified for galsulfase, velaglucerase alfa, laronidase, and imiglucerase.

Figure 1. Incremental QALY gain across sample of UODs



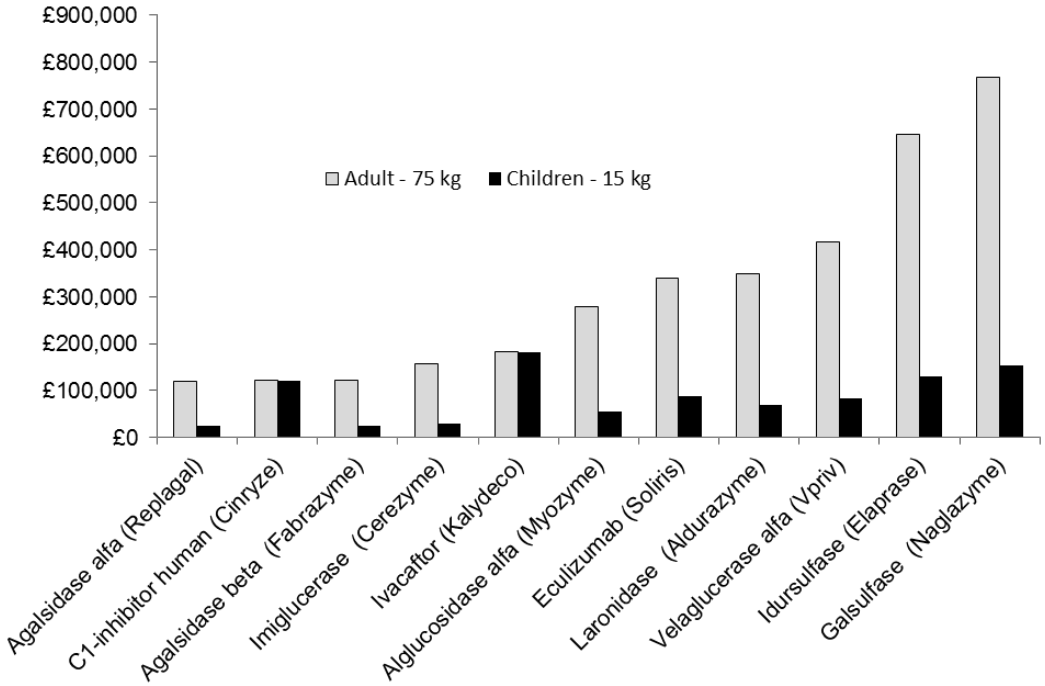
Notes:
No Data Identified (NDI) means no publicly available data have been identified.
*For the independent HTA agency review of eculizumab QALY figure, we use the ERG's estimate of 10.14 QALYs for purposes of this analysis and graphic even though this QALY gain was calculated using a flawed model that did not include excess mortality for patients in ESRD.

These findings support the statement from the Committee that eculizumab generates QALY gains "of a magnitude rarely seen for any new drug treatment". Indeed, no other ultra-orphan treatment in this cohort has been estimated (by either manufacturer or HTA agency) to have a QALY gain as great as eculizumab, even when using the lower (and flawed) estimate for eculizumab benefit calculated by the ERG. When using estimates derived from independent sources, eculizumab is seen to have a QALY gain that is over four times the median QALY increment by all other UODs and more than 50% higher than the UOD with the next highest benefit estimate (alglucosidase alfa).[6]

Figure 2 shows the annual cost for each of the UODs in the sample. As can be seen in the figure, eculizumab is in the middle of the cost distribution, both for children and for adults. Four UODs have annual costs higher than eculizumab. Interestingly, three of these four drugs do not have published data for incremental QALY gains (Figure 1).

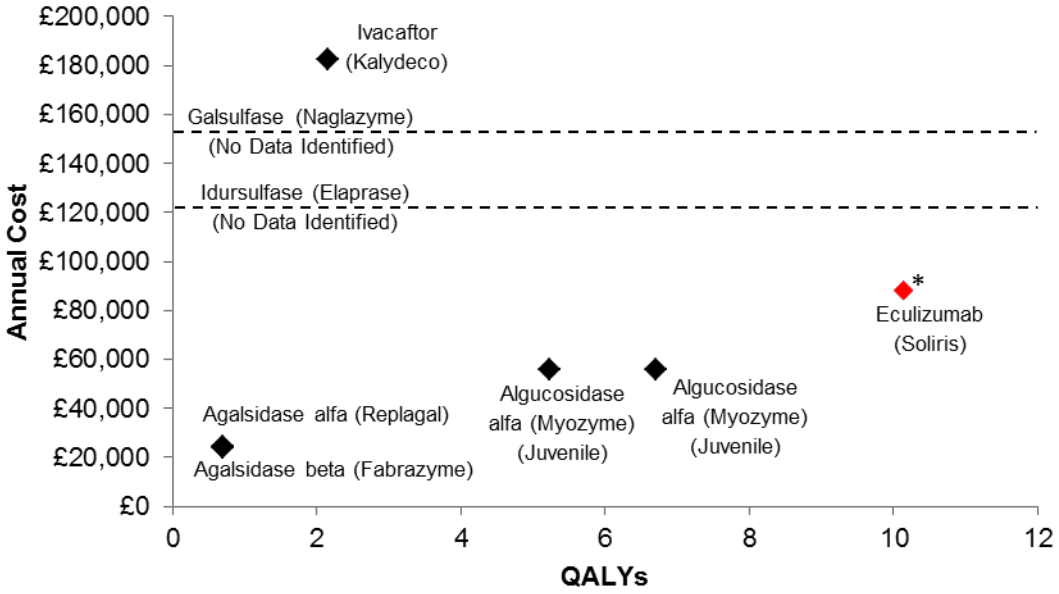
[6] Please note that two independent estimates of incremental QALY for alglucosidase alfa in early onset Pompe were identified; both are represented in Figure 1.

Figure 2. Annual cost (for Adult and Children) across sample of UODs



In Figures 3 to 6, the annual cost per UOD is mapped against the incremental QALY gained according to independent or manufacturer estimates and using child and adult annual costs. Figure 3 presents the annual child cost and QALY gain for UODs in the sample for which independent estimates of QALY gain were available. While the sample is too small to allow for inferential statistics, there appears to be a positive relationship between the annual cost of the drug and the incremental QALY gained. For example, ivacaftor has a significantly higher cost per child than eculizumab while generating less than half as many additional QALYs. Galsulfase and idursulfase are included in these figures as hashed horizontal lines due to an absence of independent data on QALY gains, but each has a higher annual price than eculizumab and so would have to generate even higher QALYs than eculizumab to be considered of equal value for purposes of NHS funding.

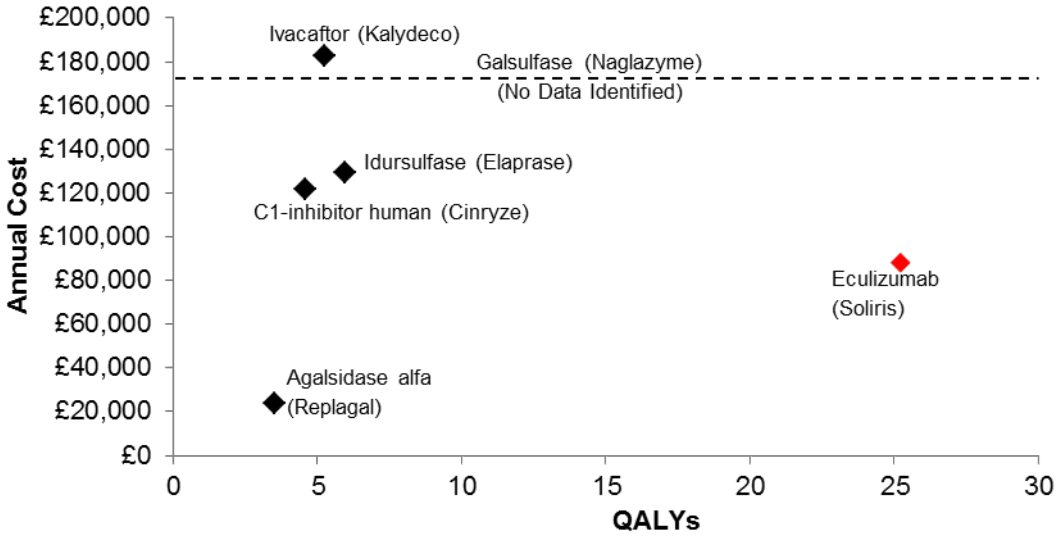
Figure 3. Annual cost (15kg child) and incremental discounted QALY gains (independent estimates)



*For the independent HTA agency review of eculizumab QALY figure, we use the ERG's estimate of 10.14 QALYs for purposes of this analysis and graphic even though this QALY gain was calculated using a flawed model that did not include excess mortality for patients in ESRD.

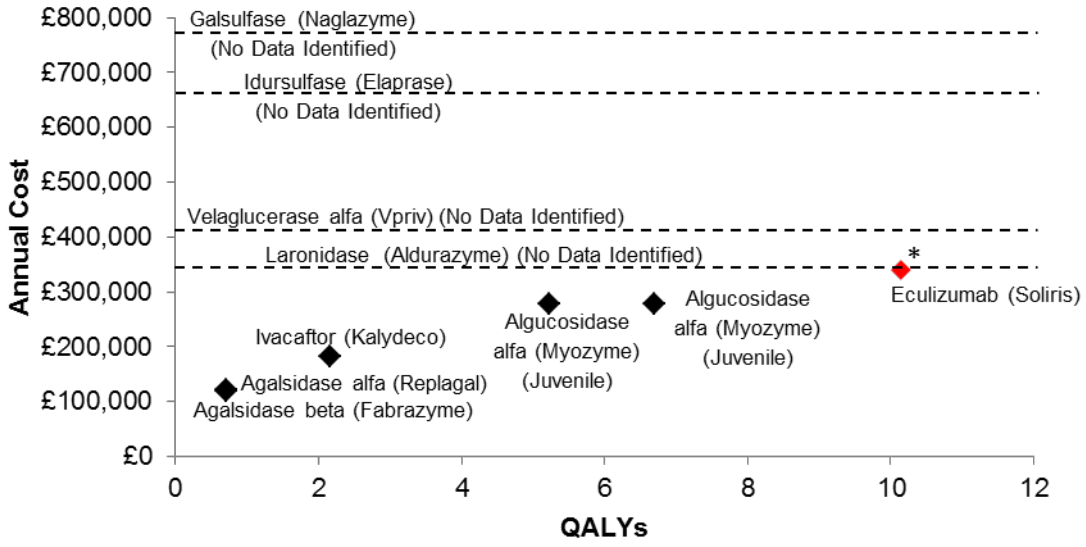
Figure 4 reproduces the same analysis, but using estimates of QALY gains as provided by manufacturers. In this analysis, eculizumab has the third lowest annual cost, but a QALY gain that is more than four times higher than the next UOD.

Figure 4. Annual cost (15kg child) and incremental discounted QALY gains (manufacturer estimates)



Figures 5 and 6 present the same information as Figures 3 and 4, except that the annual cost data are calculated for adult patients. In Figure 5, eculizumab has the highest annual cost in adult patients (laronidase, galsulfase, idursulfase, and velaglucerase are not included except as hashed horizontal lines due to lack of QALY data); however, the additional cost of eculizumab (21% higher than the second most expensive product, alglucosidase alfa) is significantly lower than the additional benefit gained with eculizumab (51% to 94% higher QALY gain with eculizumab, depending on whether the higher or lower estimate of QALY gain with alglucosidase alfa is used).

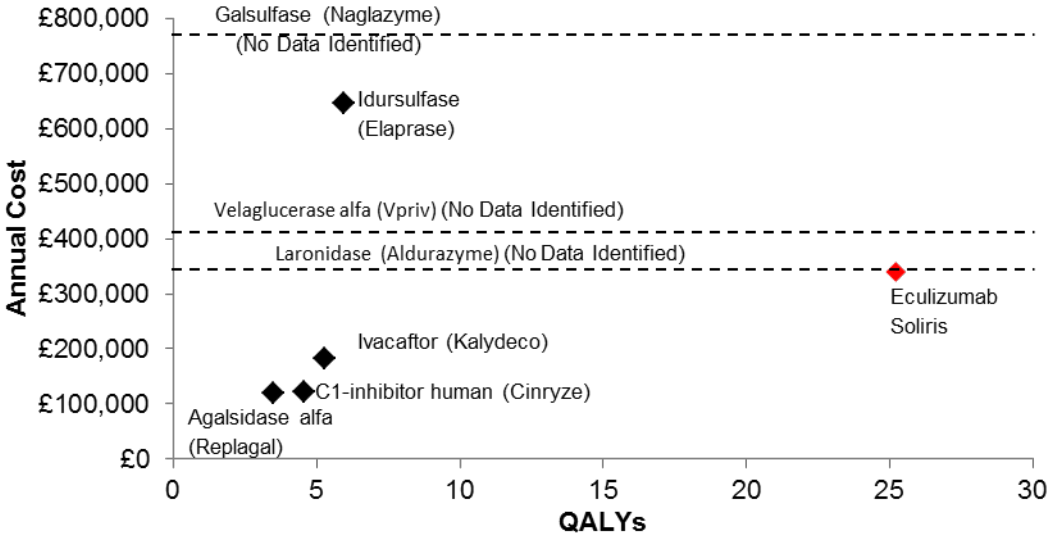
Figure 5. Annual cost (75kg adult) and incremental discounted QALY gains (independent estimates)



*For the independent HTA agency review of eculizumab QALY figure, we use the ERG's estimate of 10.14 QALYs for purposes of this analysis and graphic even though this QALY gain was calculated using a flawed model that did not include excess mortality for patients in ESRD.

Figure 6 is similar to Figure 5, but uses QALYs from manufacturer estimates. The same relationship seen in Figure 5 is witnessed with the data included in Figure 6, except that the magnitude of additional benefit gained relative to annual cost is even higher for eculizumab when using manufacturer estimates of QALY gains.

Figure 6. Annual cost (75kg adult) and incremental discounted QALY gains (manufacturer estimates)



In summary, the above analysis includes a sample of UODs that are currently commissioned and funded in England in order to compare the additional benefit associated with each drug based on publicly available and independent data, where available. The results of this analysis illustrate:

- Eculizumab for aHUS confers the highest incremental QALYs in all comparisons:
  - Where data exist, in comparisons using manufacturer QALYs, eculizumab produced 4.2 to 7.2 times the QALY gains of all comparator UOD products; and
  - Where data exist, in comparisons using independent QALYs, eculizumab produced 1.5 to 14.5 times the QALY gains of all comparator UOD products.
- Eculizumab for aHUS is in the middle-third of the distribution of annual costs for both adult and child patients compared to other UODs that are currently funded in England.
- In the four scenarios using adult or children dosing, and using either manufacturer or independent QALY estimates, eculizumab provides the greatest value for money with price within the middle third of all other funded UODs and value, shown by additional QALYs gained, exceeding by multiples all other UODs already funded in England.

Overall, based on these data and analysis, it is clear that eculizumab is an extremely effective treatment and represents very good value for money for the NHS, particularly relative to other UODs that the NHS in England currently funds. As such, the Committee has sufficient data to recommend funding eculizumab for aHUS patients in England.

V. Response to ECD Section 5.7: Concerns with NICE's Ad Hoc Budget Impact Model (BIM)

The Committee considered that Alexion's budget impact analyses may have underestimated the true rate of uptake and that the budget impact of eculizumab is "very high". The Committee, on the other hand, assumes a much larger overall budget impact for eculizumab in aHUS than estimated by Alexion (Table 5).

Table 5. Annual Estimated Cost of aHUS Treatment with Eculizumab in England (Based on ex-factory price rounded to nearest million £)

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Alexion BIM	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
NICE ad hoc BIM	£57.8	£62.5	£69.0	£75.0	£82.0

Source: NICE eculizumab ECD February 2014 and Alexion September 2013 submission, Appendix G, Table D29.

However, the inputs that NICE used for its ad hoc BIM are based on several faulty assumptions that are explained in detail below in Table 6. Specifically, in Table 6, we compare assumptions between the two models ranked by order of impact on the difference in BIM estimates. Also included is an explanation on the validity of each assumption.

Table 6. Comparison of Assumptions Used in the NICE ad hoc BIM and Alexion BIM for Eculizumab in aHUS in England

Model input or assumption	NICE ad hoc BIM	Alexion BIM	Validity perspective
Diagnosis rate	100%; unstated basis for estimate	[redacted] based on Alexion's recent experience in another ultra-rare disease, Paroxysmal Nocturnal Haemoglobinuria (PNH)	Actual diagnosis rate almost certainly below 100% as ultra-rare diseases can be difficult to diagnosis
Treatment rate	100%; unstated basis for estimate	[redacted] based on Alexion's recent experience in another ultra-rare disease, PNH	Actual treatment rate almost certainly below 100% as this requires access to special, scarce expertise
Adult/ paediatric cases	100% adults; unstated basis for estimate	[redacted], based on Alexion global experience	Clinical experts note that a substantial number of patients were paediatric patients and Committee has stated such
Discontinuation	0%; unstated basis for estimate	[redacted]	Likely an over-estimate of the actual vial consumption over time
Date of initiating therapy	New patient starts occur on first day of the year	New patient starts occur on average on the 182nd day of the year, reflecting that events will be uniformly distributed over time	Illogical that all new starts would occur on the first day of a calendar year and logical that not all new starts would occur the first day of a model year

Model input or assumption	NICE ad hoc BIM	Alexion BIM	Validity perspective
Prevalence of aHUS	170 patients; as estimated by NHS England in its interim commissioning policy	[redacted] patients, prevalence estimate is 5.5 persons per million, based on the prevalence of aHUS reported in NHS North East, as reported by Professor Tim Goodship; total prevalence based on UK population	The Alexion BIM is based on prevalence provided by an academic expert at a leading aHUS treatment centre
Annual incidence of aHUS	20 patients; based on a world-wide incidence of 0.4 per million	[redacted] patients, incidence of 0.6 per million; based on data provided by Professor Tim Goodship in 2012 and projected to reflect recent data from English aHUS cases newly diagnosed in 2013	The Alexion BIM is based on incidence provided by an academic expert at a leading aHUS treatment centre
Mortality rate of the untreated	0%; unstated basis for estimate	Background mortality rate for eculizumab patients is based on 3 years of extension data collected. SOC patient mortality rate of 8% per year is based on Coppo et al., 2010	As noted in the ECD, patients undiagnosed or receiving SOC will face a high mortality rate

To summarize, the NICE ad hoc BIM assumes a much higher, and unsupported, number of treated patients for several reasons, largely because NICE made some extreme, and unsupported, underlying assumptions that are neither practical nor logical. For example, NICE assumes a 100% diagnosis and treatment rate of aHUS prevalent patients the day that coverage and reimbursement would be conferred for eculizumab. In addition, mortality is assumed to be zero percent in the NICE ad hoc model, given that all patients are assumed to be instantly on eculizumab. Both assumptions, and the grounds purported to support them, are irrational at best and ignore the exposure of patients to this devastating disease where patients have a high rate of early death. In addition, the NICE ad hoc model assumes that all incident, new cases of aHUS occur on the first model day of the year, and are immediately diagnosed and treated, generating treatment costs for a full year for all patients. This assumption, and the grounds purported to support it, if any, are irrational at best. Surely, however, there will be a sigmoidal diffusion curve as there is with all new technology, due to a number of factors, including the difficulty in diagnosing an ultra-rare disease, the scarcity of experts who could manage treatment, and the fact patients would be diagnosed and initiate treatment at different points throughout the year, not all at the beginning of the year. This fact alone inappropriately inflates the NICE ad hoc BIM and is clearly not reflective of actual experience.

Further, the NICE ad hoc model assumes no discontinuation. However, in the ECD, the Committee stated that they were “satisfied that current use of eculizumab is being continually reviewed with the intention of achieving optimal dosing and treatment duration for each patient.” Assuming that some patients will discontinue therapy, as occurs with nearly every marketed drug, the NICE ad hoc BIM again overstates costs.

Also, the Committee stated that clinical specialists indicated that “if eculizumab is recommended for use in line with its marketing authorisation, uptake is likely to be higher than the company’s estimates” and that its great efficacy will cause faster adoption. However, in the NICE ad hoc BIM, the Committee already assumes 100% instantaneous uptake, so it is unclear how estimates could be higher than what is suggested in that model. That said, it is important to note that here again, the Committee acknowledges the clear and significant efficacy of eculizumab for aHUS, such that it concludes these efficacy benefits will result in a higher demand for therapy than that estimated by Alexion.

In conclusion, the Alexion BIM is a more plausible estimate of the total budget exposure for the NHS than the ad hoc estimate compiled by NICE as is based on realistic assumptions and experience, while the

NICE BIM appears to be largely based on assumptions that are either irrational. As such, remaining affordability concerns should be weighed in light of these facts and considerations.

VI. Clarification on Select Eculizumab-Specific Clinical Statements

As noted above, Alexion is pleased that the Committee recognizes the robust clinical effectiveness of eculizumab in the treatment of aHUS. Below, we would like to clarify a few statements included in the ECD related to duration of use of eculizumab.

Comments to ECD Sections 4.22 and 5.33: Duration of Use

In Section 4.22, the ERG expressed some concern about several limitations and uncertainties in the evidence base and, in particular, considered that the optimal dose and duration of treatment with eculizumab was unclear.

The ECD correctly cites the eculizumab SmPC which specifically and affirmatively recommends lifelong treatment with eculizumab in patients with aHUS unless discontinuation is clinically indicated.[7,8] This statement in the SmPC was issued without any request or requirement for further clinical evaluation to assess duration of treatment. We note that such a specific and affirmative EMA recommendation for lifelong treatment has not been made for other chronic therapies.

Based on evidence from the eculizumab clinical trials, the SmPC includes a risk warning for discontinuation, noting the "severe thrombotic microangiopathy complications were observed after Soliris discontinuation in the aHUS clinical studies… In aHUS clinical studies, 18 patients (5 in the prospective studies) discontinued Soliris treatment. Seven (7) severe thrombotic microangiopathy complications were observed following the missed dose in 5 patients and Soliris was re-initiated in 4 of these 5 patients."[9] This risk of complement-mediated TMA complications upon eculizumab discontinuation has been reported elsewhere since the registration trials.[10]

While the ERG report (pgs. 63-64) cites the aHUS UK evidence submission regarding potential prospective studies to investigate duration of treatment[11], the ERG report goes further to state that they have no evidence to verify that flexible dosing can be carried out successfully.[12,13] As described in Alexion's initial submission, chronic complement inhibition is necessary to block terminal complement in

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[7] Atypical haemolytic uraemic syndrome (aHUS) - eculizumab: evaluation consultation document; NICE. Available at http://www.nice.org.uk/guidance/highlyspecialisedtechnologyevaluations/atypicalhaemolyticuraemicsyndrome/EvaluationConsultationDocument.jsp.

[8] European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) for Soliris. 2014.

[9] European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) for Soliris. 2014.

[10] Alachkar, N, et al. Transpl International, 2012; 25(8); e93-e95. Chátelet, V, et al. Transpl Proc, 2010; 42 (10): 4353-4355. Köse, Ö, et al. Sem Thromb Hemost, 2010; 36(6): 669-672. Mache, CJ, et al. Clin J Am Soc Nephrol, 2009; 4(8): 1312-1316; Vilalta, R, et al. Pediatr Nephrol, 2012; 27(12): 2323-2326.

[11] Atypical haemolytic uraemic syndrome (aHUS) - eculizumab: evaluation report; 06 - Consultee submission - aHUS UK Part 2; aHUS UK. Available at http://www.nice.org.uk/guidance/highlyspecialisedtechnologyevaluations/atypicalhaemolyticuraemicsyndrome/EvaluationConsultationDocument.jsp?domedia=1&mid=72E55146-9FAB-F6C2-8CB85D0A734E96B1. pg 9.

[12] Atypical haemolytic uraemic syndrome (aHUS) - eculizumab: evaluation report; 19 - Evidence Review Group Report prepared by ScHARR; ScHARR. http://www.nice.org.uk/guidance/highlyspecialisedtechnologyevaluations/atypicalhaemolyticuraemicsyndrome/EvaluationConsultationDocument.jsp?domedia=1&mid=72E55146-9FAB-F6C2-8CB85D0A734E96B1

[13] Atypical haemolytic uraemic syndrome (aHUS) - eculizumab: evaluation report; 06 - Consultee submission - aHUS UK Part 2; aHUS UK. Available at http://www.nice.org.uk/guidance/highlyspecialisedtechnologyevaluations/atypicalhaemolyticuraemicsyndrome/EvaluationConsultationDocument.jsp?domedia=1&mid=72E55146-9FAB-F6C2-8CB85D0A734E96B1

aHUS due to the intrinsic genetic complement defects that are the underlying mechanisms of disease causing chronic complement activation and systemic TMA in aHUS.[14] Removal of complement inhibition carries a risk of severe complications associated with complement-mediated TMA.[15] Accordingly, there is no recommendation for discontinuation or modification of dosing included in the interim NHS Commissioning Policy, which in fact states that eculizumab "treatment is for life."[16]

Comments to ECD Section 5.4: Current "Stopping Criteria"

The Committee noted from the evidence submitted by clinical specialists that very specific criteria are followed when starting treatment with eculizumab and circumstances in which eculizumab treatment should be stopped have been defined. The Committee heard from the clinical specialists that all patients have treatment with eculizumab for the first 8 weeks until results of their genetic tests are available. Treatment is then adjusted or stopped based on the test results. The Committee was satisfied that current use of eculizumab is being continually reviewed with the intention of achieving optimal dosing and treatment duration for each patient.

While the clinical specialist's evidence submission cited by the ECD report speculates on the potential for treatment modification based on individual patient characteristics such as genetic test results, there have been no controlled trials to demonstrate that this can be carried out safely. There exists no systematic clinical evidence that eculizumab treatment can be adjusted or stopped in patients with aHUS. In contrast, as mentioned above, existing medical evidence demonstrates that removal of complement inhibition carries risk of TMA complications in patients with aHUS.[17] The need for lifelong treatment to block terminal complement in patients with aHUS has been previously validated by CPAG and included in the interim NHS clinical commissioning policy.[18] The dosing schedule described in the SmPC and in the manufacturer's submission was based on prospective controlled clinical trials and prior pharmacokinetic studies determining the necessary eculizumab dose needed to completely block terminal complement in aHUS. As noted in the ECD report, the SmPC specifically and affirmatively recommends lifelong treatment with eculizumab in patients with aHUS; such a specific and affirmative EMA recommendation for lifelong treatment has not been made for other chronic therapies. We also want to point out to NICE the ethical and potential legal challenge of contravening direct, specific, and affirmative regulatory direction.

VII. Comments to the Matters in Paragraph 14 of the Interim Process

Below, we provide comments specific to the issues raised in paragraph 14 of the HST Interim Process from May 2013.

a) Whether all the evidence available to the Committee has been appropriately taken into account.

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[14] Atypical haemolytic uraemic syndrome (aHUS) - eculizumab: evaluation report; 02 - Submission by the technology manufacturer - Alexion; Alexion Pharmaceuticals. Available at http://www.nice.org.uk/guidance/highlyspecialisedtechnologyevaluations/atypicalhaemolyticuraemicsyndrome/EvaluationConsultationDocument.jsp?domedia=1&mid=72E55146-9FAB-F6C2-8CB85D0A734E96B1

[15] European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) for Soliris. 2014.

[16] Clinical Commissioning Policy Statement: Eculizumab for atypical haemolytic uraemic syndrome; NHS England. http://www.england.nhs.uk/wp-content/uploads/2013/09/e03-hss-a.pdf.

[17] European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) for Soliris. 2014.

[18] Alachkar, N, et al. Transpl International, 2012; 25(8); e93-e95. Châtelet, V, et al. Transpl Proc, 2010; 42 (10): 4353-4355. Köse, Ö, et al. Sem Thromb Hemost, 2010; 36(6): 669-672. Mache, CJ, et al. Clin J Am Soc Nephrol, 2009; 4(8): 1312-1316; Vilalta, R, et al. Pediatr Nephrol, 2012; 27(12): 2323-2326.

Alexion has confirmed, earlier in this document, that we believe the clinical evidence available to the Committee has been appropriately analysed and that the many positive conclusions made by the Committee properly reflect the available scientific evidence.

However, we remain concerned that the Committee failed to consider the information provided by Alexion in relation to value for money and budget impact. Specifically, the assumptions relied upon by the Committee for the purposes of its assessment of BIM are wholly inconsistent with the available evidence and the CIC data provided by Alexion was not taken into account by the Committee in reaching its conclusions regarding whether eculizumab should be recommended for use in NHS patients. To be clear, we believe that the assumptions made in the NICE ad hoc BIM and the grounds purported to support it, if any, are not rational and reflect a wilful disregard of the facts.

b) The summaries for benefits and costs are reasonable interpretations of the evidence.

Alexion accepts the Committee's summaries of the effects associated with eculizumab therapy, although we agree with its conclusion that the assessments do not fully take account of all the benefits of the treatment. However, we reiterate our concerns above with the Committee's approach to the assessment of budget impact, which is based on inappropriate data and over estimates the impact of expected eculizumab use within the NHS. As previously stated, we believe that the assumptions made in the NICE ad hoc BIM and the grounds purported to support it, if any, are not rational and reflect a wilful disregard of the facts.

c) The provisional recommendations are sound and constitute a suitable basis for guidance on national specialised commissioning.

While, as indicated above, Alexion agrees with the Committee's conclusions regarding the clinical benefits of therapy with eculizumab, for reasons explained above, we do not believe that the Committee's conclusions with respect to the budget impact of eculizumab therapy are consistent with the available evidence, or that the Committee's refusal to recommend eculizumab for use in NHS patients outlined in the ECD, represents a sound basis for guidance. Indeed, and as previously stated, we believe that the assumptions made in the NICE ad hoc BIM and the grounds purported to support it, if any, are not rational and reflect a wilful disregard of the facts. In particular, while the Committee has recognised the high clinical need of patients with aHUS and the "step change" in treatment associated with eculizumab, it is unclear how these matters have been taken into account in view of the Committee's refusal to recommend eculizumab at the ECD stage even though its costs are comparable with those of other ultra-orphan products funded by the NHS and the benefits exceed all other HSTs identified by Alexion.

d) Whether there are any equalities related issues that need special consideration that are not covered in the ECD.

Alexion is aware of no equalities related issues that have not been addressed.

VIII. Comments on Procedural Matters

Alexion has sought to engage fully with NICE in relation to this HST evaluation and accordingly we have notified the Institute promptly of procedural concerns as these arise, including concerns relating to undisclosed conflicts of interest by the ERG and Deloitte, as well as several procedural deficiencies propagated throughout review and consideration. For the sake of completeness, we summarise briefly the very substantial procedural concerns that we have in relation to the conduct of this evaluation and potential implications for the overall fairness of the process.

a) Lack of transparency in relation to the evidence relied upon by the Committee in formulating and in relation to their preliminary decision.

In a number of areas, the evidence relied upon by the Committee in formulating the ECD has not been disclosed to Alexion and in other circumstances, the reasoning that forms the basis of the Committee's conclusions is unclear, absent, or not rational. These matters are inconsistent both with NICE's procedures and a fair process and we would therefore request at this stage, that the lack of transparency is corrected and that Alexion is provided with adequate opportunity to consult in relation to these matters before a final decision is reached by the Committee.

- At paragraph 5.8 of the ECD, the Committee states that it "was made aware of the annual costs of a range of other treatments that are available through nationally commissioned specialised and highly specialised services". The list of such other treatments and the information provided to the Committee was not disclosed to in the evaluation report and is not known to Alexion.
- At paragraph 5.11, the ECD states that the Committee "seeks further information from NHS England on what considerations relating to the management of its specialised commissioning budget it considers should be taken into account when determining a reasonable overall treatment cost for eculizumab". The information, if any, provided by NHS England in response to this request has not been made available to Alexion, even though it is clearly of fundamental importance in determining how Alexion would have wished to respond to the ECD.
- Also at paragraph 5.11, the ECD states "the Committee acknowledged ongoing work initiated by NICE to develop a set of cost reference points for highly specialised treatments compared with other treatments commissioned through specialised services". The text indicates that this work by NICE would be made available before the next Committee meeting. Again, this information has not yet been made available to Alexion and the company is prejudiced by the fact it has had no opportunity to consider NICE's work or to comment on it in the context of this consultation procedure.
- NICE's ad hoc BIM is largely based on data, the evidence for which has not been disclosed, including:

    - Rate of diagnosis of aHUS,
    - Treatment rate for aHUS,
    - Proportion of aHUS cases who are adults,
    - Proportion of patients who discontinue treatment during the first year, and
    - Mortality rate of untreated patients,

    Alexion disagrees with the figures used by NICE for all of these parameters, but in the absence of any reference as to the evidence sources used by NICE, is prejudiced in its ability to respond to and challenge the assumptions relied upon by the Committee for the purpose of its conclusions on budget impact of eculizumab treatment.

b) The procedure for this evaluation is uncertain and developments during the process have prejudiced eculizumab.

Eculizumab is the first HST to be evaluated by NICE using the new procedure and, while the Interim Process was issued before the commencement of the evaluation, this is imprecise and the approach to evidence, including the methodology to be applied by the ERG is unclear.

A clear process is a fundamental part of a fair procedure. In this case however, it is only clear that the process is continuing to be developed (as demonstrated by the fact that the fundamentally flawed [redacted] report will be produced only after consultation on the ECD, towards the end of the process). This has prejudiced eculizumab in circumstances where the evidence submission by Alexion (prepared in

accordance with directions from NICE) could not address criteria that has not been identified, where the Committee has not been informed of the procedure applicable to HSTs and where the ERG did not appear to understand the approach required in the context of an HST evaluation.

c) ScHARR did not produce an ERG report appropriate for this evaluation, reflecting the instructions issued by NICE.

In advance of this HST evaluation, we assumed that ScHARR had seen and considered the Interim Process as well as the report template provided by NICE, detailing the proper approach to preparation of an ERG report. We are aware that ScHARR raised various questions with NICE regarding the procedure to be followed in the context of an HST evaluation, although not, to our knowledge in relation to the approach to the economic analysis.

However despite the fact that NICE's report template and the Interim Process make clear that a "value for money" or "cost consequence" approach is appropriate in the context of an HST evaluation, ScHARR followed a standard health technology appraisal cost utility methodology, calculating incremental cost effectiveness ratios (ICERs) even though these had not been presented by Alexion (Alexion had explicitly been asked not to follow this methodology or present such data in its submission) and was not consistent with the approach directed by NICE. The result of this error by ScHARR is that it was highly critical of Alexion for failing (as it thought) to prepare an appropriate submission and this has unfairly coloured the conclusions of the ERG report and, in our view the views of the Committee.

Secondly, the ERG reference Alexion's submission to AGNSS in its report, even though AGNSS had approached the assessment of eculizumab in a different way from that proposed by NICE and Alexion had again explicitly been requested by the Institute not to include material from the AGNSS submission in its materials presented to NICE. Again, this approach by ScHARR was unfair; it allowed ScHARR to refer to material which Alexion had been prevented from referencing or explaining.

d) The [redacted] report, commissioned towards the end of the evaluation process and in the context of substantial procedural deficiencies, raises concerns of unfairness even if not directly relied upon by the Committee.

We have referred to our substantial concerns in relation to the preparation of the [redacted] report, including the haste with which it was developed, the incompleteness of the research conducted, the lack of transparency in relation to evidence sources relied upon, the fact that the analysis and conclusions have not been subject to consultation and the possibility (which we are currently unable to assess) that conflicts of interest may have prejudiced the fairness and validity of the preparation of the report, and the assessments and conclusions presented.

While NICE has reassured us that the report will not be relied upon for the purposes of the evaluation of eculizumab for aHUS, we are aware that it has been circulated to the Committee and other Consultees who have been asked to comment on the report. Without instructions otherwise from NICE, the Consultees may refer to this report or use it as a basis for considerations in their submissions and we therefore have continuing concerns that it may still influence the Committee's approach to this evaluation - an outcome that would be both unfair and unreasonable.

IX. Conclusion

Again, Alexion is pleased that Committee has recognized that eculizumab is an extremely effective treatment for patients with aHUS, and that the use of eculizumab would be of significant value to patients in England with this life-threatening disorder who have no other treatment options. Furthermore, we feel strongly that any remaining affordability concerns are effectively mitigated both through recognition of the

more accurate and realistic budget impact estimates provided by Alexion than those in the ad hoc BIM developed by NICE as well as the overall expenditure protections put into effect by the DH and the ABPI through the November 2013 PPRS agreement.

Given the strong clinical endorsement of eculizumab by the Committee, combined with the exceptional value of eculizumab illustrated in comparison to existing UODs currently funded by the NHS, we look forward to receiving a positive decision by the Committee so that the few patients in England with aHUS can continue to receive access to eculizumab, the only EMA-approved treatment for this devastating disease.