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Prevalence and prognosis of paroxysmal nocturnal haemoglobinuria and the clinical and cost-effectiveness of eculizumab

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Prevalence and prognosis of paroxysmal nocturnal haemoglobinuria and the clinical and cost-effectiveness of eculizumab treatment

A WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION REPORT

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the National HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS:

Martin Connock and Dechao Wang undertook the reviews of natural history, prevalence/incidence and clinical effectiveness, undertook the economic evaluations and wrote these and other sections of the report. Anne Fry-Smith performed all literature searches. David Moore led the project, contributed to all sections and edited the final report.

CONFLICTS OF INTEREST:

None

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SUMMARY

***Objectives*:** To review the evidence on the prevalence, natural history and prognosis of paroxysmal nocturnal haemoglobinuria (PNH) and to systematically review the clinical effectiveness and cost- effectiveness of eculizumab (Soliris®) treatment.

Background: PNH is a rare disease characterised by chronic intravascular haemolysis associated with reduced life expectancy, diminished quality of life and serious complications including anaemia, fatigue, thrombosis, difficulty swallowing, erectile dysfunction, recurrent abdominal pain, pulmonary hypertension, chronic kidney disease and subclinical thrombosis. PNH is genetically acquired by mutation of the PIG-A gene in a bone marrow stem cell. This leads to deficiency or absence of certain cell surface proteins that protect red blood cells (RBCs) from complement attack and subsequent haemolysis. Standard treatments are supportive including blood transfusion. Eculizumab is a new treatment for PNH which targets the root cause of haemolysis by blockading complement and thwarting complement-induced haemolysis. Eculizumab "*is indicated for treatment of patients with PNH but evidence of benefit is limited to patients with a history of transfusion".* It is administered by IV infusion weekly for 4 weeks, then every other week. Annual cost of treatment is £252,000 in year one and £245,700 thereafter.

Prevalence: A single study in the UK reported an annual incidence of 0.13/100,000. Using incidence and survival data the calculated prevalence was 1.59/100,000 which is within the limit of <20/million defining an ultra-orphan disease. In the West Midlands the predicted number of patients is about 87.

Natural history and prognosis: PNH can occur at any age (median diagnoses at 30 - 40 years, range 0.5 - 81 years). Patients proceed to serious complications, including anaemia, thrombosis, haemorrhage, acute myeloid leukaemia, impaired kidney function, bone marrow failure and premature death. Presentation and sequence of events varies from patient to patient. A proportion (15-25%) may achieve spontaneous remission. A history of aplastic anaemia is common (about 30% in European studies). Thrombosis is the major identified cause of death. Thromboses occur in a variety of abdominal veins and also in arteries; an average of reported thrombosis rates is 4.22/100 patient years and median time from diagnosis to thrombosis varies from 2 to 5 years. Reported median survival after diagnosis for European patients varied from 10 to 16 years; more recent cohorts have better survival. Prognostic factors associated with the progression to death and severe disease include: thrombosis at diagnosis or follow-

up, evolution to pancytopenia, myelodysplasia, acute leukaemia, advance age, severe leukopenia/neutropenia at diagnosis, severe infection, and renal failure.

Clinical effectiveness of eculizumab: Evidence of effectiveness and safety of eculizumab comes from a 26 week placebo controlled RCT with 87 patients (TRIUMPH), a 52 week uncontrolled study with 97 patients (SHEPHERD), and an ongoing study (EXTENSION). All participants in these trials had a history of transfusions. Eculizumab significantly reduced haemolysis, anaemia and transfusion requirement. Patient scores in the FACIT-fatigue and EORTC quality of life questionnaires improved relative to baseline. In the RCT 51% of patients on eculizumab and 0% receiving placebo remained independent of packed RBC transfusion, the units-transfused were reduced by ~70% with eculizumab but unchanged by placebo. Eculizumab, but not placebo, greatly reduced mean lactate dehydrogenase (LDH) levels indicating considerable diminution in haemolysis. The most common adverse events (AEs) were headache, upper respiratory tract infection and viral infection. In SHEPHERD, the longest study, during 1 year of treatment there were 44 serious adverse events of which 7 were judged possibly related and none probably or definitely related to eculizumab. In the last 26 weeks of SHEPHERD most AEs occurred at rates comparable to the placebo arm of TRIUMPH. In the first 26 weeks headache occurred at high frequency; the rate subsided in the second 26 weeks to below that in the TRIUMPH placebo arm. The numbers and severity of infections was similar to those in the placebo arm of TRIUMPH. Compliance was good; 92 of 96 patients in SHEPHERD elected to continue treatment beyond 52 weeks. No patient withdrew from eculizumab due to side effects. Retrospective analysis of medical notes of 195 patients in the ongoing EXTENSION study indicated eculizumab effected a 7 fold reduction in the rate of thrombosis from 7.37/100 patient years pre-treatment to 1.07/100 patients years during treatment. The EXTENSION study provided evidence that eculizumab treatment was associated with an improvement in, or prevention of worsening of, kidney function.

Cost-effectiveness of eculizumab: Literature searches failed to identify any economic analyses of PNH treatments. Furthermore a lack of reliable quantitative information means a fully informed estimation of cost-effectiveness for PNH patients with a history of transfusions is impractical at this time. Therefore we conducted three preliminary economic evaluations: I) Based on RCT evidence, the incremental cost-effectiveness ratio (ICER) for use of eculizumab vs. no use of eculizumab is ~£257,100 per patient

with stabilised haemoglobin, ~£340,500 per patient with normalised LDH level, and ~£132,500 per patient with LDH level less than twice the upper normal limit.
II) Under the assumptions that eculizumab returns survival to normal, that median survival in standard care (SC) of patients eligible for eculizumab is between 10 and 27 years, that annual cost of SC is between £1K and £100K per patient, and that up to 90% of SC cost is avoided by use of eculizumab, the ICER ranged from about £0.5M to £1.4M/life year gained (LYG). III) Based on reported thrombosis rates and mortality rates from thrombosis, and a time horizon of 10 to 15 years, the estimated ICERs ranged from £1.2M to £1.4M/LYG for patients like those in clinical trials and £2.8M/LYG to £3.2M/LYG for all diagnosed PNH patients.

Budget impact: Based on published prevalence and incidence estimates and assuming between 16% and 33% of PNH patients are treated with eculizumab with annual savings from SC costs avoided ranging from £1K to £10K/patient, the budget impact for the West Midlands (population ~ 5.5M) is estimated to be between about £3.3M and £7.0M in year one and £9.5M to £15.3M by year 10. If greater savings of between £100K and £200K are made from standard care treatments avoided then at 10 years annual cost ranges between about £1.8M and £9.1M.

Conclusions

- The prevalence of PNH in the UK lies within the limit that defines an ultra-orphan disease.
- Thrombosis is a major cause of death. From 3 European studies an average thrombosis rate corresponded to 4.22 per 100 patient years.
- Studies of cohorts of European PNH patients indicate the median survival after diagnosis ranges from ~10 to ~27 years. More recently studied cohorts have better survival.
- For haemolytic patients with a history of transfusions recruited to trials eculizumab was highly effective at reducing haemolysis and transfusion requirement. It improved quality of life, reduced anaemia and diminished the rate of thrombosis about 7 fold.
- Preliminary analysis suggests that the ICER for eculizumab versus SC likely lies between £0.5M and £1.4M per life year gained for patients like those recruited to clinical trials and between £2.8M and £3.2M per life year gained for all diagnosed patients.

ABBREVIATIONS AND ACRONYMS

Abbreviation / Acronym	Definition
AEs	Adverse events
C5	Complement factor C5
CRD	NHS Centre for Reviews and Dissemination, University of York
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPO	Erythropoietin
FACIT	Functional Assessment of Chronic Illness–Fatigue
FCA	Flow cytometric analysis
GFR	Glomerular filtration rate
GPI	Glycosylphosphatidylinositol
HRQOL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IQR	Inter quartile range
IV	Intravenous
LDH	Lactate dehydrogenase
LYG	Life years gained
MCK	Major clinical kidney events
NICE	National Institute for Health and Clinical Excellence
NO	Nitric oxide
Py	Patient years
PIG-A	Phosphatidylinositolglycan-class A
PNH	Paroxysmal nocturnal haemoglobinuria
QALY	Quality adjusted life year
QOL	Quality of life
RBC	Red blood cells
RCT	Randomised controlled trial
SAEs	Serious adverse events
SC	Standard care
SPC	Summary of product characteristics
WHO	World Health Organisation

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FIGURES

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APPENDICIES

1. AIM OF THE REPORT

This report aims to address the following questions about paroxysmal nocturnal haemoglobinuria (PNH):

1. What is the incidence and prevalence of PNH?
2. What is the natural history and prognosis of PNH?
3. What is the clinical effectiveness of eculizumab (Soliris®) in the treatment of PNH?
4. What is the cost-effectiveness of eculizumab (Soliris®) in the treatment of PNH?

Questions 1 and 2 are addressed by narrative review and questions 3 and 4 by systematic review of the available evidence.

2. BACKGROUND

Paroxysmal nocturnal haemoglobinuria is a rare acquired haematological disorder characterised by circulating red blood cells (RBCs) that are unusually susceptible to haemolysis. Patients may experience anaemia, fatigue, thromboses which can be life threatening, recurrent abdominal pain, erectile dysfunction and difficulty swallowing. More severely effected PNH patients have under-diagnosed chronic kidney disease, pulmonary hypertension and subclinical thromboses (personal communication). Several recent narrative reviews describe the disease, its pathogenesis and clinical management.[1-3]

2.1 Aetiology of PNH

The cause of PNH is somatic mutation in the X-linked PIG-A gene of a stem cell in the bone marrow. PIG-A function is obligatory for the assembly of glycosylphosphatidylinositol-anchored proteins (GPI-anchored proteins) that are found on the external surface of cells. It has been suggested the PNH progenitor cells derived from a PIG-A mutant stem cell can gain a relative growth advantage over their normal counterparts. The consequence of this is that PNH cells deficient in GPI-anchored proteins can become predominant amongst mature circulating blood cells of all cell lineages (see below).

The CD59 and CD55 cell surface GPI-anchored proteins protect host cells from the terminal products of complement activation which can assemble to form a "membrane attack complex" (MAC) capable of puncturing the cell membrane and allowing the escape of soluble intracellular products. In PNH the lack or deficiency of C59 on the surface of RBCs renders them highly susceptible to the MAC with resultant haemolysis and the release of cell contents such as haemoglobin and lactate dehydrogenase (LDH). Other PNH cell lineages are less susceptible to MAC possibly due to a shorter life span, active metabolic turnover of cell membrane or presence of additional protective surface proteins. As complement is in a state of continuous low level activation, PNH patients are continually susceptible to haemolysis. "Brisk episodes" of haemolysis (paroxysms) coincide with increases in complement activation following infection, stress, strenuous exercise, or excessive alcohol intake. Such episodes can result in sufficient loss of haemoglobin to discolour the urine.[4] Chronic and paroxysmal haemolysis contribute to anaemia and fatigue experienced in PNH. Anaemia may become sufficient to necessitate transfusion of packed RBCs.

Excess thrombosis in PNH is thought to be contingent upon haemolysis.[5] Extra-cellular haemoglobin is a potent scavenger of nitric oxide (NO) which has major roles in vascular homeostasis including smooth muscle and platelet function. Haemoglobin and arginase released from RBCs deplete NO, the former by radical scavenging, the latter by removal of arginine the feeder substrate for NO production. NO depletion then leads to impaired regulation of vascular smooth muscle tone, altered platelets, and changes in endothelial cells. The latter may result in conditions favourable for local vasoconstriction, platelet aggregation and activation, and intravascular thrombosis. It is possible that GPI-protein deficient platelets may also promote thrombosis. Depletion of NO is a likely cause of erectile dysfunction and dysphagia in PNH via effects on smooth muscle.[6]

It is thought that all patients with PNH have an underlying bone marrow failure (commonly aplastic anaemia) in which haematopoiesis may be suppressed by the immune system via a postulated interaction dependent on the presence of GPI-linked protein(s).[2,6] Since the mutant PNH cells lack such proteins they would have a selective advantage and this could explain how a single mutant stem cell, greatly

outnumbered by other stem cells, can contribute a significant proportion of the mature blood cell population in the circulation. Although females have two PIG-A genes, one on each X-chromosome, one will be inactivated early in development by X chromosome inactivation. The probability of somatic PIG-A mutation in the active X-chromosome in females is thought to be the same as that for the single X-chromosome in males. Therefore the frequency of PNH amongst males and females is expected to be equal.[6]

2.2 Diagnosis of PNH

PNH patients may present with haemoglobinuria, thrombosis, anaemia, abdominal pain or other clinical symptoms. Modern diagnosis uses flow cytometric analysis (FCA) of blood cells. When tagged with appropriate fluorescent antibodies specific for GPI-anchored proteins PNH cells that are wholly or partially deficient in GPI-anchored proteins emit different fluorescent intensities to each other and also to normal (non-PNH) cells. FCA identifies and quantifies the differently fluorescent populations of normal and GPI-deficient cells. Three types of RBCs can be detected: Type I cells, which are normal; Type II cells which are partially deficient in GPI proteins; Type III cells which lack GPI proteins. The relative proportions of RBC types will reflect the bone marrow's contribution of the PNH clone relative to normal clones, the severity of the individual's PIG-A mutation and haemolysis which will deplete Type II and III RBCs, and the individuals transfusion history which will raise the proportion Type I RBCs. Transfusions do not alter the granulocyte profile so the ratio of PNH granulocytes to normal granulocytes is a good indicator of the clonal contribution of the PNH cell line.

2.3 Current Service provision

There appear to be no published guidelines for treatment of PNH. The most common treatments deal with anaemia.[1-3] Different severities of anaemia have been defined by World Health Organisation (WHO) and by National Cancer Institute (NCI) according to blood haemoglobin levels (see Table 1).[7]

Table 1 Grading systems for anaemia

Severity	WHO haemoglobin levels	NCI haemoglobin levels
Grade 0	≥ 11.0 g / dl	Within normal limits (12 – 16 g / dl)
Grade 1	9.5 – 10.9 g / dl	> 10.0 g / dl to within normal limits
Grade 2	8.0 – 9.4 g / dl	8.0 – 10.0g / dl
Grade 3	6.5 – 7.9 g / dl	6.5 – 7.9 g / dl
Grade 4	< 6.5 g / dl	< 6.5 g / dl

In PNH, anaemia may result from haemolysis (which will fluctuate according to complement activation) or from impaired erythropoiesis. Standard treatment employs folic acid (5mg/day) to stimulate RBC production by the bone marrow. The blood reticulocyte count gives an indication of the bone marrow's capacity to respond to the anaemia. Haemolysis may deplete the patient's available iron and dietary supplementation may be required. Genetically engineered erythropoietin (normally produced mainly by the kidneys) has been used to stimulate RBC production[8]; a typical course of treatment with erythropoietin costs about £ 5,000.[9]

In general where the underlying cause of anaemia is not amenable to specific treatment, or where specific treatment will take some time to take effect and the need to reverse anaemia is urgent then blood transfusions are considered.[9] Guidelines have been published.[10,11] PNH patients who experience severe anaemia with symptoms (see Appendix 1) may require blood transfusion.

The cost to the NHS to collect and produce one unit of RBCs for transfusion was estimated to be £120 in 2004[12]; costs have been rising because of increased screening due to concerns about safety, so that 2008 cost is likely to be greater. The cost of RBC transfusion (2.7 units on average) was estimated at £635 in 2000/01[13]; this estimate included cost to transfusion services and the cost of hospital stay for transfusion and is likely to apply to PNH patients. Frequent transfusion carries small risk of infection (e.g. from prions or from human immunodeficiency virus) and of immune reaction; these risks will vary according to the quality control exercised by transfusion services.

Other treatments for PNH that may be considered include corticosteroids, thought by some to suppress haemolysis, anti-coagulants (warfarin, heparin) to reduce the incidence of thrombosis, analgesics for abdominal pain, and sildenafil for dysphagia or erectile dysfunction. Most patients will benefit from these supportive measures.

Allogeneic haematopoietic stem cell transplantation, to replace the mutant and faulty bone marrow cells with normal counterparts, is currently considered the only potentially curative therapy. Few PNH patients have been treated in this way because of the high risks involved and the scarcity of suitable donors.

2.4 Description of eculizumab (Soliris®)

The development of eculizumab provides a new therapeutic option for PNH patients and one that is targeted at blocking haemolysis. Eculizumab is a monoclonal antibody. It reduces intravascular haemolysis by binding and inactivating the complement factor (C5) responsible for triggering the production of the MAC which destroys the sensitive RBCs of PNH patients. The early events of complement activation are unaffected by blockade of C5, so eculizumab therapy should have little effect on function of the early part of the complement cascade.

In 2007 the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMEA) recommended the granting of marketing authorisation for eculizumab, the first medicinal product for human use to be evaluated by accelerated assessment.[14]

Eculizumab is a full sized humanised IgG monoclonal antibody to human complement factor C5 with no cross reactivity for non-human C5. It is generated in a mouse cell line and so the carbohydrate component is of murine origin.

When bound to their antigen some IgG antibodies activate complement and bind to Fc receptors on scavenger cells promoting clearance of IgG-antigen complexes. Eculizumab has been genetically engineered to lack both these properties ensuring that C5-binding does not initiate complement activation and providing a relatively extended half life in the vascular compartment.[4]

According to the EMEA Scientific Discussion document and the Summary of Product Characteristics eculizumab is indicated “for treatment of patients with PNH but evidence of benefit is limited to patients with a history of transfusions”.[15] This indication is difficult to interpret since “a history of transfusions” is ill-defined.

According to expert clinical opinion UK use has been limited to frankly haemolytic PNH patients who as a consequence of haemolysis require transfusions. This represents 2.4 patients per million of the general population (personal communication). In the West Midlands (population taken as 5.5 million) this equates to 13 patients. Guideline criteria that define those patients who are frankly haemolytic and who would qualify for eculizumab have not yet been developed but plans to do so are under consideration (personal communication).

Eculizumab is available in 300 mg vials and is administered by IV infusion over 25 to 40 minutes during an initial induction phase at one 600 mg dose weekly for four weeks, followed a week later by a 900 mg dose every other week. The dose regimen aims to maintain plasma eculizumab levels above 35 μg/mL which achieves blockade of C5.

One 300 mg vial of eculizumab costs £3,150.[16] With the dose regimen described above the first year of treatment would cost £252,000 and subsequent years £245,700. The manufacturer is planning to fund the delivery and administration of eculizumab via a third party homecare provider for PCTs and patients using the drug. An application has been made for National Commissioning Group funding to run a Central PNH service in the UK (personal communication).

Late phase complement factors protect against infection by encapsulated bacteria (e.g. *Neisseria meningitidis*, *Haemophylus influenzae*) but are blocked by eculizumab. Patients who receive the drug must first be vaccinated against meningococcus.

Treatment is likely to be life-long for the majority of patients, or until superior treatment becomes available. Some patients may spontaneously go into remission after a period of chronic disease (see section 4.2.1); such patients would no longer require eculizumab. Since decisions about NHS support of eculizumab treatment are pending and considering the fact that the drug has just achieved marketing licence, it is impossible to assess the present or future degree of diffusion.

3. REPORT METHODS

3.1 Incidence, prevalence, natural history and prognosis review methods

Prospective or retrospective studies were sought that investigated the incidence, prevalence, prognosis or natural history of PNH. Relevant publications were those detailing incidence and prevalence, progress of clinical features, disease bio-markers, quality of life (QOL) and survival information, in defined populations with PNH that predated the introduction of eculizumab or in which treatment with eculizumab was excluded. Studies with sample size less than 20 and/or with follow-up less than 3 years were not considered.

Searches were carried out which incorporated appropriate search terms; full search details are provided in Appendix 2 . Retrieved references were scrutinized by one reviewer and full publications sought of potentially relevant studies identified on the basis of title and/or abstract.

Methodological quality of the selected studies was assessed informally using guidance published by the Centre for Research and Dissemination (CRD).[17] Data was extracted from relevant studies by one reviewer. Evidence available was analyzed and synthesized into narrative reviews. Particular emphasis was placed on studies from the UK or elsewhere in Europe.

3.2 Clinical and cost-effectiveness systematic review methods

A search was undertaken to identify systematic reviews and primary studies about the clinical effectiveness of eculizumab in the treatment of PNH and any economic studies on the use of eculizumab in the treatment of PNH. Details of the search strategy are provided in Appendix 2.

Searches were not limited by language. Inclusion criteria for effectiveness studies were:

- Study design: RCTs, controlled studies, before and after studies in at least 10 patients
- Intervention: eculizumab

- Comparator: any (for before and after studies and extensions to controlled studies the comparison was with outcome measures taken before eculizumab administration)
- Outcomes: any

Abstracts of studies subsequently published as full papers were excluded.

Study selection was undertaken independently by two reviewers. Disagreements were resolved by discussion. Information on study characteristics, study quality and results for each study was extracted by one reviewer and checked by a second reviewer. Where required, information was extracted from published graphs (Appendix 3). Data extraction discrepancies were resolved by discussion.

Study quality was assessed according to the Centre for Research and Dissemination (CRD)[17]guidelines for consideration of threats to validity arising from selection, performance, attrition and detection biases. The checklist items for RCTs were: randomisation, allocation concealment, blinding, comparability of groups, follow-up of trial participants, handling of missing data (intention-to-treat analysis), power calculation. Study quality was assessed by one reviewer and checked by a second. Discrepancies were resolved by discussion.

The small number of studies and their varied study designs precluded formal pooling in meta-analyses. Information extracted from effectiveness studies was reported by narrative review.

As the licence for marketing eculizumab in Europe was issued in 2007 the number of published economic studies was likely to be small, therefore the following broad inclusion criteria were used: any fully published primary economic study reporting costs or cost-effectiveness of treatment of PNH patients. Study selection and data extraction was undertaken by one reviewer and checked by another. The quality of studies was to be assessed with the checklist of Drummond and Jefferson.[18]

4. RESULTS

4.1 Incidence and prevalence

The search of electronic databases did not yield any published studies of incidence or prevalence of PNH. One study presented as a poster and abstract was identified by scrutinising reference lists of published studies.[19] This study, dated June 2007, was described as "the first to accurately report the incidence and prevalence of PNH". The geographical study area encompassed a large part of north eastern England and cases were collected from 1991 to 2006. Cases were diagnosed at a single reference laboratory using flow cytometric detection of PNH red cells and neutrophils; case ascertainment was likely to be good. In 14.5 years 76 cases were diagnosed in a population estimated to be 3,742,835. This gives an incidence of 0.13/100,000/year. Based on incidence and survival rates (unspecified) the 15 year prevalence was given as 1.59/100,000. This places PNH within the definition of an ultra-orphan disease as advised by NICE. Most patients (82.5%) had evidence of haemolysis; however according to expert opinion (personal communication) only ~2.4 patients per million of population (100 x 2.4/15.9 = 15% of PNH patients) would be sufficiently haemolytic to warrant eculizumab treatment.

Taking the West Midlands population to be approximately 5.5 million and using the above figures we would expect a prevalence of about 87 PNH patients in the region. Thus according to expert opinion (see above) 13 or 14 patients would currently require eculizumab. This number would be annually supplemented by one newly diagnosed patient. The proportion of current patients untreated with eculizumab who will progress to require treatment is unclear.

Summary of prevalence

- A single study, conducted in the UK, reported the prevalence of PNH to be 1.59/100,000.
- The prevalence of PNH falls within the limit of < 2/100,000 that NICE advise to be a cut off defining an ultra-orphan disease in the UK.
- This prevalence indicates the existence of approximately 87 PNH patients in the West Midlands.

4.2 Natural history and prognosis

The searches retrieved a total of 324 articles. The titles and abstracts were scanned and 14 articles were selected and obtained in full. Five of them contained information relevant for review of natural history and prognosis of PNH.[20-24] The remaining seven studies were not considered due to little information or no data relevant to European patients.[25-31] In addition two further studies[32,33] were included for survival data, one of which was published as a poster only.[33] The major characteristics and outcomes of these studies are listed in Table 2.

Table 2 Main features of natural history and prognosis studies

Author *Study year* [Country] *Study Design*	Population *Female %* [Sample Size]	Age at diagnosis (yrs) Median (range) *Diagnosis*	Follow-up (yrs) Median (range) *Diagnosis yrs*	Treatment(s)	Outcome
Hall[20] *2003* [UK] *Prospective*	With PNH *Not report*ed [N = 163]	33 (0.5 - 85) *NR*	Median: 6 Range: 0.2-38	Prophylaxis with warfarin (24%)	Proportion of thrombosis 18% (29/163) Median time of thrombosis from diagnosis, median (range) 4.75 (0.3-15) years Proportion of Leukaemia 1% (2/163) Death rate due to PNH 70% (14/20)
Hillmen[21] *1995* [UK] *Partly Prospective*	PNH hospital referrals 1940-1970 *Not report*ed [N = 80]	42 (16 - 75) *Ham's test* ¥¥	Range: 0-48 *Diagnosed 1940-1970*	Supportive measures, e.g. Oral anticoagulant, Transfusions.	Proportion of thrombosis 39% (31/80) Proportion of clinical remission 15% (12/80) Median survival 10 year Proportion of survival 25 years 28% (22/80) Death rate due to PNH (venous thrombosis or haemorrhage) 58% (28/48)
Socie[22] *1996* [France] *Prospective*	With PNH *55%* [N = 220]	*NR* *Ham's test* ¥¥	Maximum 39, Median 6.7 *Diagnosed 1950-1995*	Androgens, Danazol, Immuno-suppressive therapy, Low-dose corticosteroids, BMT, Transfusions	Proportion of thrombosis 27% (59/220) Median time of thrombosis from diagnosis, median (range) 2.1 (0-22) years 8-year cumulative incidence rate of thrombosis (SE) 28% (4) 8-year cumulative incidence rate of Leukaemia (SE) 1% (1) 8-year cumulative incidence rate of Pancytopenia (SE) 15% (3) 8-year cumulative incidence rate of Myelodysplastic syndrome (SE) 5% (2) Median survival, year (95%CI) 14.6 (11,19.2)
Ware[23] *1991* [USA] *Retrospective*	Young PNH patients (age ≤ 21 years) *50%* [N = 26]	14.3 *CLS test*	0-19	*NR*	Proportion of bone marrow failure at present 58% (15/26) compared to 25% for adults Median survival, year (95%CI) 13.5 Death rate 38% (3/8)
Moyo[24] *2004* [USA] *Retrospective*	With PNH *50%* [N = 49]	34 (6.3 - 80.7) *Ham's test* ¥¥	*NR*	*NR*	Proportion of thrombosis 29% (14/49) Death rate due to PNH 67% (6/9) Proportion of death due to thrombosis 67% (6/9)
Used for survival analysis only					
Gramont,[33] *.1985* [France] *Retrospective*	With PNH¥ 56.3% [N = 151]	*Ham's test* ¥¥	NR *Diagnosed 1950-1981*	Androgens, Corticosteroids, Transfusions Heparin	Death rate 30% (51/151) Median survival 13 years Renal insufficiency 8.6% (7.3% severe). 32.5% present with thrombosis
Latour,[32] *2006*, [France] *Retrospective*	With PNH *54%* [N = 478]	34 (IQR 24 - 47) *Ham's test* ¥¥ */ CLS*	5.6 *Diagnosed 1950-2005*	BMT (10.4%)	96 died. Kaplan-Meier survival: 85% at 5 yrs, 75% at 10 yrs, 66% at 15 yrs

¥ French speaking patients. ¥¥ Ham's test; BMT: Bone marrow transplantation; CLS, complement-lysis sensitivity; SE: standard error; *NR* = not reported.

Of the natural history/prognosis studies three were prospective cohorts[20-22] and two studies were retrospective cohorts.[23,24] The follow-up period of PNH patients varied from 0 to 48 years. The studies by Hall[20] and by Socie[22] had a median follow-up of 6 to 7 years. Other studies did not report the median follow-up period. However, the study by Hillmen[21] provided a detailed course of illness of all 80 PNH patients, which allowed an estimate of median follow-up (6-7 years) for this study. Three studies[22-24] reported the gender of PNH patients and each suggest an equal male:female ratio. Three studies[20-22] reported the treatment for PNH patients, which included prophylaxis with warfarin, supportive measures (such as oral anticoagulant therapy), transfusion, androgens, immunosuppressives, low-dose corticosteroids, danazol, and bone-marrow transplantation.

A large Chinese study (N=476) was identified.[34] The reported male:female ratio of 5.3:1 was strikingly different to that reported for European populations. Other differences included an earlier onset of disease, lower rate of thrombosis and higher rate of anaemia (98% with anaemia and 38.3%with aplastic anaemia). As the rates of clinical manifestations in PNH were dissimilar to those in European studies conclusions based European studies may not be applicable to populations with a significant proportion of people of Chinese / East Asian origin.

4.2.1 Natural history

From the included studies above it is clear that PNH is a life threatening disease associated with a range of debilitating morbidities. The complications of PNH include thrombosis, hepatic failure (probably due to thrombosis), haemorrhage, renal failure (caused by intravascular haemolysis), evolution to pancytopenia, myelodysplasia, anaemia, acute myeloid leukaemia, impaired kidney function, bone marrow failure, and death.[20-24,35,36] Some patients experience spontaneous remission.[21]

Aplastic anaemia and transfusions: Two studies reported that 29% (23/80)[21] and 30% (65/220)[22] of patients received a diagnosis of aplastic anaemia before the diagnosis of PNH. The median time between diagnosis of aplastic anaemia and positive PNH diagnosis was estimated to be 3 years.[22] As part of initial treatment, 75% (164/220)[22] of patients had red blood cell transfusions, which reflected the severity of patients' haemolysis and the extent of bone marrow dysfunction.

Thrombosis: Three prospective and one retrospective study gave details on thrombosis. Thrombosis occurred most strikingly in the abdomen, such as in hepatic veins, splanchnic veins, but also occurred in cerebral venous vessels, isub-dermal vessels, limb vessels, and other unusual venous sites. Arterial thrombosis was rare.[35] The median age at time of thrombosis was 32 years (range, 1-76 years).[20] The proportion PNH patients with thrombosis varied from 18% to 39%;[20-22,24] Hall[20] reported 18% (29/163), Hillmen[21] 39% (31/80), Socie[22] 27% (59/220). The median (range) time of thrombosis from diagnosis was 4.75 (0.3-15) years in the study by Hall[20] and 2.1 (0-22) years in the study by Socie.[22] The retrospective study by Moyo[24] reported a thrombosis rate of 29% (14/49), but no follow-up or treatment information was provided. The summary results of the three prospective studies[20-22] gave an average thrombosis rate of 26% (Appendix 4). This corresponds to 4.22 per 100 patient years, if a median follow-up of 6.4 years is used.[20-22]

The summarised thrombosis rate is consistent with that reported from other studies. For example, a review paper by Rosse[35] stated that patients with PNH are markedly prone to venous thrombosis and that about 30 to 40% of patients of European descent have some form of thrombosis. The study by Nishimura[37] reported that thrombosis was significantly more prevalent in white patients (31.8%, 56/176) than Asian patients (4.3%,9/209). However, haematopoietic failure was less prevalent in white patients (33%, 58/176) than Asian patients (36.4%,76/209) (difference not statistically significant). The study by Dunn reported that 8% (3/40) of Chinese PNH patients had complication of thrombosis.[28]

Spontaneous remission: Few studies reported a clinical remission of PNH patients. The study by Hillmen[21] reported 15% (12/80) PNH patients had spontaneous remission that occurred between 10 and 20 years after diagnosis of PNH. No prognostic factors (e.g. severity of symptoms, complications, and the proportion of red cells sensitive to lysis) could be identified for remission. A possible explanation for remission may be that the clones of PNH-affected cells have a finite life span and the presence of normal stem cells enables repopulation of the bone marrow.[21] The study by Zhang[38] reported that about 25% of the PNH patients achieved long-term clinical remission in both the UK and the Chinese groups.

Acute leukaemia: The rate of acute leukaemia is very rare. The study by Socie[22] reported that the mean 8-year incidence rate of acute leukaemia was 1% with a standard error of 1. The time of acute leukaemia from diagnosis was 1-3 years. The review paper by Rosse[35] stated that about 2-3% of patients with PNH had acute leukaemia usually within five years of onset of PNH.

Survival: The medial survival after diagnosis has been estimated to be about 10 to 15 years in both adults and children. About a quarter of the PNH patients survive 25 years or more.[21-23,35]

Hillmen compared survival of a cohort of UK PNH patients, referred between 1940 and 1970 and followed to 1994, with that for the general population matched by age and sex. Median survival was found to be 10 years from diagnosis of PNH and the difference between PNH patients and general population over 25 years equated to an average loss of 10.17 life years due to PNH (Figure 1, left). Figure 1 also shows survival curves for several European cohorts found in the literature. Median survival results ranged from about 10 to nearly 30 years with more recent cohorts having better survival. Possible explanations include chance, improved diagnosis resulting in inclusion of less severe cases, improving standards of care, or less probably, different disease characteristics between European populations.

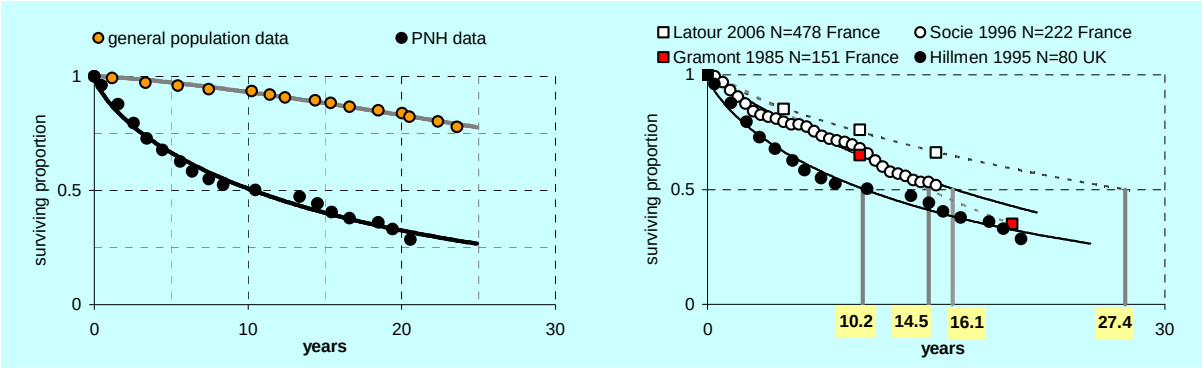

Figure 1 Survival reported for European cohorts of PNH patients.

UK cohort (Hillmen,1995[21]) left panel; European cohorts right panel: Hillmen,1995[21], Socie,1996[22], Latour,2006[32] , Gramont,1985[33]. Considerable extrapolation beyond data required for Latour 2006. Curves fitted according to Weibull distributions.

The death rate related to PNH varied from 38% to 70%.[20,21,23,24] However, some studies[23,24] did not report the follow-up periods. A PNH related death rate was estimated to be 60-70% with a median follow up period of 6-7 years.[20,21] Survival analysis revealed a similar death rate (22%) for Western PNH patients and Asian

patients (21%).[37] However, the causes of death were different. The proportions of PNH patients that died of thrombosis were 29-42% for the western patients[21,37] and 6-8% for the Japanese patients.[37,39] Japanese patients had a longer mean survival time (32 vs. 19 years), although Kaplan-Meier survival curves were not significantly different.[37] The proportions of PNH patients that died of haemorrhage were 6-23% for the western patients,[21,39] and 39%[39] for the Japanese patients. The higher incidence of haemorrhagic death in Japanese patients was suggested might be related to thrombocytopenia by hypoplastic bone marrow.[39]

4.2.2 Prognostic factors

Adverse prognostic factors include thrombosis at diagnosis or follow-up, evolution to pancytopenia, myelodysplasia, acute leukaemia, advance age (>55) at onset, severe leukopenia/neutropenia at diagnosis, severe infection as a complication, and renal failure.[35,37] The identification of these prognostic factors might help the design of prospective clinical trials for PNH.

Summary of natural history and prognosis

- PNH may occur at any age from infancy through to old age, with a high incidence in young adulthood. The age at diagnosis varies from 0.5 to 85 years, with a median of 30 to 40 years.
- PNH patients proceed to serious complications, which include anaemia, thrombosis, haemorrhage, acute myeloid leukaemia, impaired kidney function, bone marrow failure, and death. The sequence of PNH varies from patient to patient. A proportion (15-25%) of PNH patients might achieve long-term clinical remission. An average of reported thrombosis rates is 4.22 per 100 patient years; reports of the median time of thrombosis from diagnosis vary from 2 to 5 years. Thrombosis is the major identified cause of death. About 1-3% of patients with PNH may develop acute leukaemia within five years since diagnosis of PNH.
- Median survival after diagnosis for European cohorts varied between about 10 and 27 years, and appeared superior the more recent the cohort. For a UK cohort followed from 1970 to 1994 median survival after diagnosis was 10 years; loss of life years from PNH averaged about 10.2 years across a 25 year time span.

- As PNH is a rare disease with complex aetiology and expression, investigations into the natural history of PNH are ongoing.
- Prognostic factors associated with the progression to death and severe diseases have been identified. They are: thrombosis at diagnosis or follow-up, evolution to pancytopenia, myelodysplasia, acute leukaemia, advance age (> 55 years), severe leukopenia/neutropenia at diagnosis, severe infection, and renal failure.

4.3 Systematic review of effectiveness of eculizumab

4.3.1 Studies: yield, characteristics and quality.

Searches of bibliographic databases yielded 273 hits (Medline 45, Medline in process 50, Embase 170 and Cochrane library 8). Full paper copies of 18 potentially relevant studies were obtained. Two further relevant publications were identified by scanning the reference lists of relevant articles. A recently presented poster and a submitted poster were provided by the authors. Of the full publications obtained 5 satisfied the inclusion criteria (see Appendix 5). The two posters were also included. The excluded studies are listed in Appendix 5 with reasons for exclusion. The main characteristics of the included studies are shown in Table 3.

Table 3 Main characteristics of included studies

STUDY [study sites]	STUDY DESIGN	Duration (weeks)	Sample size	POPULATION	Median Age (years)	Male %	OUTCOMES
PILOT **Hillmen (2004)**[40] **Hill (2005)**[41] [NR]	Before/after prospective with extension	12 + 52	11	≥4 transfusions in last 12 months 8/11 AA	48	55	PNH RBCs Haemolysis (LDH) Transfusions QOL [EORTC C30] Adverse events
TRIUMPH **Hillmen (2006)**[42] [34]	RCT multinational Stratified by previous transfusion units	26	43 eculizumab 44 placebo	≥4 transfusions in last 12 months Platelets > 100 x 10^9/L 18/87 with AA	35 placebo 41 eculizumab	40	Transfusions; Hb-level Haemolysis (LDH) PNH RBCs QOL [EORTC C30] Adverse events
SHEPHERD **Brodsky (2008)**[43] [33]	Before / after prospective	52	97	≥1 transfusion in last 2 years Platelets > 30 x 10^9/L	41	49	Adverse events Transfusions; Hb-level Haemolysis (LDH) Thrombotic events QOL [EORTC C30] Fatigue [FACIT}
EXTENSION **Hillmen (2007a)**[44] [NR]	Before/after (retrospective/ prospective) extension study	281 patient years of eculizumab	195	Combined from 3 previous studies	NR‡	NR‡	Thrombotic events Haemolysis (LDH)
POSTERS							
EXTENSION **Hillmen (2007b)**[36] [NR]	Before/after (retrospective) Post hoc analysis	NR	193‡‡	Combined from 3 previous studies	39 (18 to 45)	46	Change in CKD stage Time to MCK event MCK event rate
Hill (2008) unpublished [NR]	Before/after	84 days	164	Combined from TRIUMPH and SHEPHERD	NR	NR	Change in FACIT score compared with cancer patients given EPO

DOSE REGIMEN: The dose regimen was the same in all studies; 600 mg eculizumab weekly for 4 weeks then 900 mg every 14 days (in SHEPHERD 6 patients required 900 mg every 12 days to achieve C5 blockade). ‡ Median age and male female ratios for patients in contributory studies were reported separately. ‡‡ Baseline data provided for 193 patients. AA = aplastic anaemia; CKD = chronic kidney disease; EORTC = European Organisation for Research and Treatment of Cancer instrument. EPO=erythropoietin; FACIT = Functional Assessment of Chronic Illness Therapy-Fatigue instrument; LDH = plasma / serum lactate dehydrogenase activity; MCK event = major clinical kidney event; NR = not reported; QOL= quality of life.

The five full publications and the two posters reported outcomes for about 200 patients treated with eculizumab in four industry sponsored studies: a phase two PILOT study,[40,41] a multi-national double blind placebo controlled randomised trial, TRIUMPH;[42] a multinational before and after trial, SHEPHERD;[43] and a multinational ongoing open label EXTENSION study so far published in one full paper, Hillmen 2007a,[44] and in one poster, Hillmen 2007b.[36] The study populations all had a history of transfusion to a greater or lesser extent; what proportion of the total PNH population these patients represent is uncertain. The dose regimen for the intervention was the same in all studies: induction with four 600mg doses weekly followed by a 900 mg dose every other week. A few patients (one in TRIUMPH, six in SHEPHERD) required small increases in dose frequency. Outcomes reported focussed on measures of haemolysis and anaemia, the requirement for transfusions, quality of life, thrombotic events and safety / adverse events.

In the PILOT study eleven patients with a history of transfusion (median age 48 years, 6 men and 5 women) were treated with eculizumab. Outcome measures were reported for before treatment and after 12 and 64 weeks of treatment.[40,41] TRIUMPH[42] was a 26 week double blind RCT that randomised 87 participants aged > 18 years to either placebo (n=44) or eculizumab (n=43). Patients had a history of transfusions (≥ 4 transfusions in last year) with established PNH (range 0.5 to 38.5 years duration; median: placebo 9.2 years eculizumab 4.3 years). Twenty-one percent had a history of aplastic anaemia. The one year uncontrolled multi-centre SHEPHERD[43] study recruited 97 patients with a history of transfusions; this population had required less transfusions than in TRIUMPH (1 transfusion in last 2 years rather than 4 in last 12 months) but participants could have platelets levels as low as 30 x 10^9/L compared to 100 x 10^9/L in TRIUMPH. About 70% of SHEPHERD participants would not have qualified for TRIUMPH (47% had too few transfusions, 36% too low platelets, and 12% both too few transfusions and too low platelets). The ongoing open label EXTENSION study[44] has included patients from the preceding PILOT, TRIUMPH and SHEPHERD studies.

Study quality

The quality of TRIUMPH was good and is summarised in Table 4 .

Table 4 Quality assessment of the TRIUMPH RCT.

Criterion	
Randomisation	Performed centrally using an interactive voice system.
Allocation concealment	Used an interactive voice-response system
Blinding	Described as double blind; persons blinded not described.
Intention to treat analysis	Yes
Power calculation	Yes
Difference at baseline	Twice as many placebo patients (27%) with history of aplastic anaemia
Total dropouts Intervention	2/43; one for pregnancy, one for inconvenience of travel to study centre.
Total dropouts Control	10/44; perceived lack of efficacy

The PILOT and SHEPHERD studies were uncontrolled prospective open label investigations that reported before-eculizumab versus after-eculizumab measures. With this study design it is difficult to determine if the changes observed are treatment-dependent or would have happened anyway in the absence of treatment. When before-after differences are very great and/or when they occur rapidly, and if there are no independent reasons for suspecting large fluctuations, the probability they might have occurred in the absence of an intervention is diminished. The authors used analyses at multiple time points during treatment and, in SHEPHERD,[43] comparison with the placebo group of the TRIUMPH study as partial solutions to this problem. The validity of latter strategy can be questioned since the populations in the two studies differed with respect to pre-study transfusion rates and platelet levels (see above).[42] In the SHEPHERD study of 97 patients enrolled 96 completed (one withdrawal) and 92 chose to continue with the intervention. The number of patients contributing to EORTC QOL scores was not clear but otherwise all 96 continuing patients contributed outcome data. The authors' estimate of statistical significance of change from baseline was described as a mixed-model analysis with base-line scores as a covariate, time as fixed effect and patients as random effect.

The Hillmen EXTENSION study[44] of rates of thrombosis before and after treatment included 195 patients. Rates of thrombosis prior to receipt of eculizumab were calculated by retrospective analysis of patient histories by the principle investigator at each study centre, while post-treatment rates were monitored prospectively during the trials. This procedure was necessary because of the short duration and small

patient numbers in the TRIUMPH RCT yielded too few thrombosis events (1) for any reliable comparison between placebo and intervention.

There was insufficient methodological detail to judge the quality of the posters.

4.3.2 Clinical trial results

The results for the PILOT[40,41] study were consistent with but superseded by the much larger TRIUMPH, SHEPHERD and EXTENSION studies and therefore are not considered further here (for details of results see Appendix 6). In the following sections trial results are reviewed by outcome.

Transfusion rate and haemoglobin level (summarised in Figure 2)
In TRIUMPH patients had received ≥ 4 transfusions in the previous 12 months. Twenty-one percent had a history of aplastic anaemia. The stated primary outcomes of the TRIUMPH RCT were: stabilisation of haemoglobin levels and units of packed red cells transfused. Each patient was assigned a transfusion algorithm according their 12 month pre-trial transfusion history. This specified the number of transfusion units to be administered for a given level of haemoglobin should this be below the set level. Transfusions were undertaken if the patient showed symptoms of anaemia and was below the set level. Seventeen clinic visits were scheduled during the 26 week trial.

At end of follow-up 49% (21/43) patients in the eculizumab group had maintained haemoglobin above their set point (median set point 7.7 g/dl) in the absence of transfusions. None of the placebo group achieved this end point ($p < 0.001$). Time to first transfusion was significantly shorter in the placebo group than the eculizumab group ($p < 0.001$; Figure 2). Mean haemoglobin level held steady in the eculizumab group,10 ± 0.2 g/dl at baseline to 10.1 ± 0.2 at week 26, but decreased in the placebo group 9.7 ± 0.2 at baseline to 8.9 ± 0.2 at week 26, ($p <0.001$; Figure 2). This is despite more units of RBCs transfused in the placebo group

The median number of units transfused during treatment was significantly lower in the eculizumab group compared to placebo ($p<0.001$); eculizumab median 0 (IQR 0 to 6); placebo median 10 (IQR 6 to 16). For the placebo group the mean units of

packed RBCs transfused during trial (9.7; SE 0.7) was little different to that calculated for 26 weeks pre-trial (11.0; SE 0.8). In contrast the eculizumab group exhibited reduced units transfused (mean units decreased from 9.6, SE 0.6 pre-treatment to 3.0, SE 0.7 during treatment). During the trial, patients on placebo received a total of 482 units compared to 131 for the eculizumab group; in the six months prior to trial the groups received about the same total of transfusion units, 417 and 413 respectively; (see Figure 2 for all these findings)

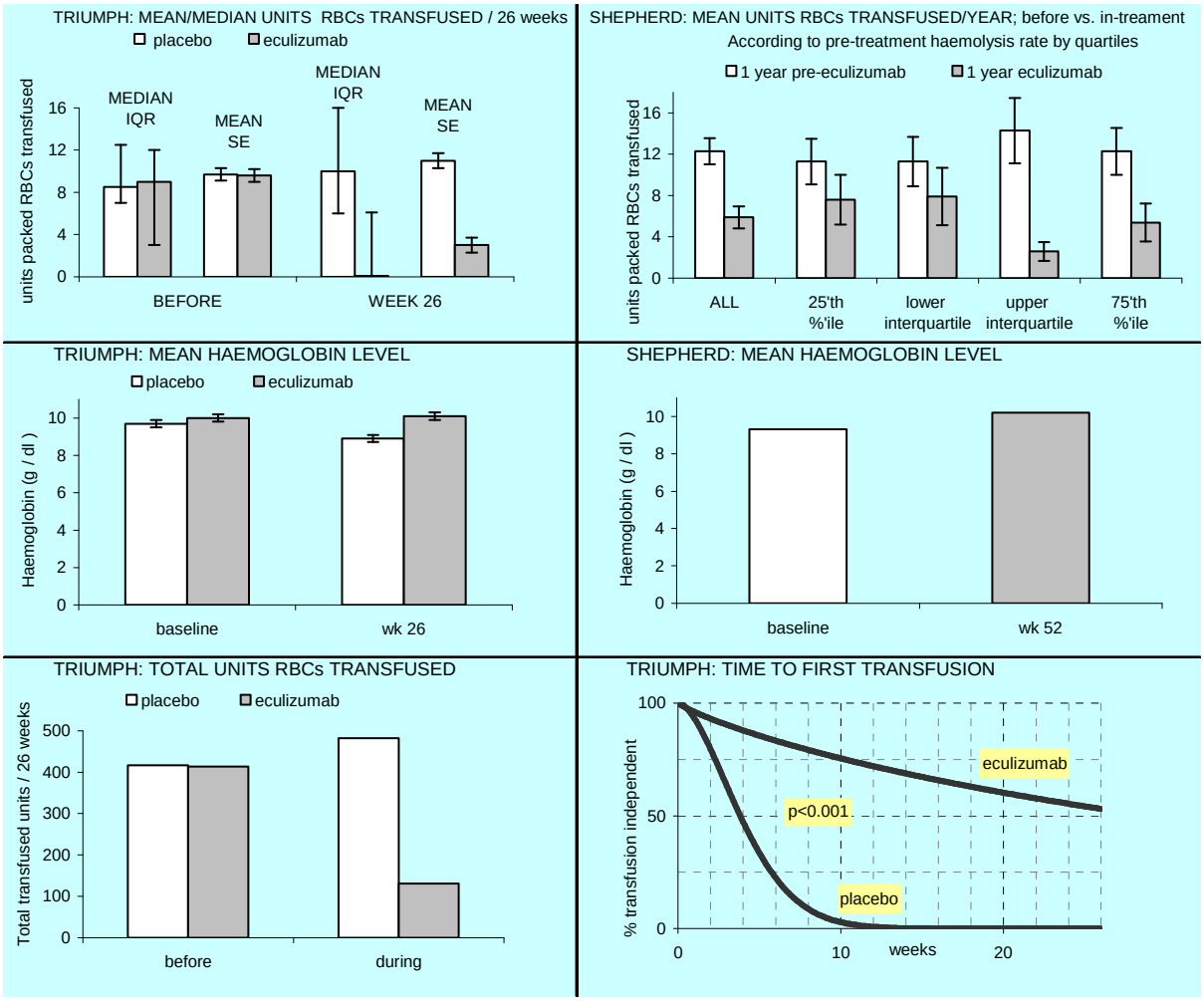

Figure 2 Summary of transfusion and haemoglobin results.

Error bars are SE unless stated otherwise. Participants were: TRIUMPH placebo=44, eculizumab=44; SHEPHERD N= 97. Results for the PILOT study are given in Appendix 6. .

The population in the SHEPHERD study had received fewer transfusions than in TRIUMPH (≥ 1 transfusion in last 2 years rather than ≥ 4 in last 12 months). Transfusion results broadly confirmed those in TRIUMPH. Fewer units of packed RBCs were transfused/patient during 52 weeks of treatment (mean 5.9 ± 1.25) than during the 52 weeks prior to treatment (mean 12.3 ± 1.25). The mean units in 52 weeks of treatment compares to the mean in 26 weeks of treatment in TRIUMPH

(5.9:3). Patients who at baseline were classified in the upper inter-quartiles with respect to haemolysis (based on LDH measures) required less transfusion during the treatment period than did those in the interquartiles with less haemolysis at baseline (Figure 2). Fifty one percent of SHEPHERD patients were reported to be transfusion independent during 52 weeks of treatment, however the proportion of patients transfusion-free for the 52 weeks prior to treatment was not stated. Mean haemoglobin was slightly higher at week 52 than at baseline Figure 2 .

Haemolysis *(results summarised in Figure 3)*

In TRIUMPH haemolysis was defined as a secondary outcome. Markers for haemolysis were LDH levels and proportion of circulating PNH type III RBCs. The placebo group mean LDH level remained high throughout the TRIUMPH study, 2258 ± 154.8 U/L at baseline and 2418.9 ± 140.3 at week 26, whereas the mean level fell with eculizumab treatment, from 2199.7 ± 157.7 at baseline to 327.3 ± 67.6 at week 26 (Figure 3). The reduction in LDH with eculizumab treatment commenced within one week, and from 4 weeks onward mean levels were only moderately above the normal range of 103 to 223 U/L. Levels were in normal range for 15/41 of the eculizumab group and none of the placebo group. The median values for area under the LDH curve was significantly different ($p < 0.001$) between groups (58,587 vs. 411,822 U/L over 182 days respectively for eculizumab and placebo groups).

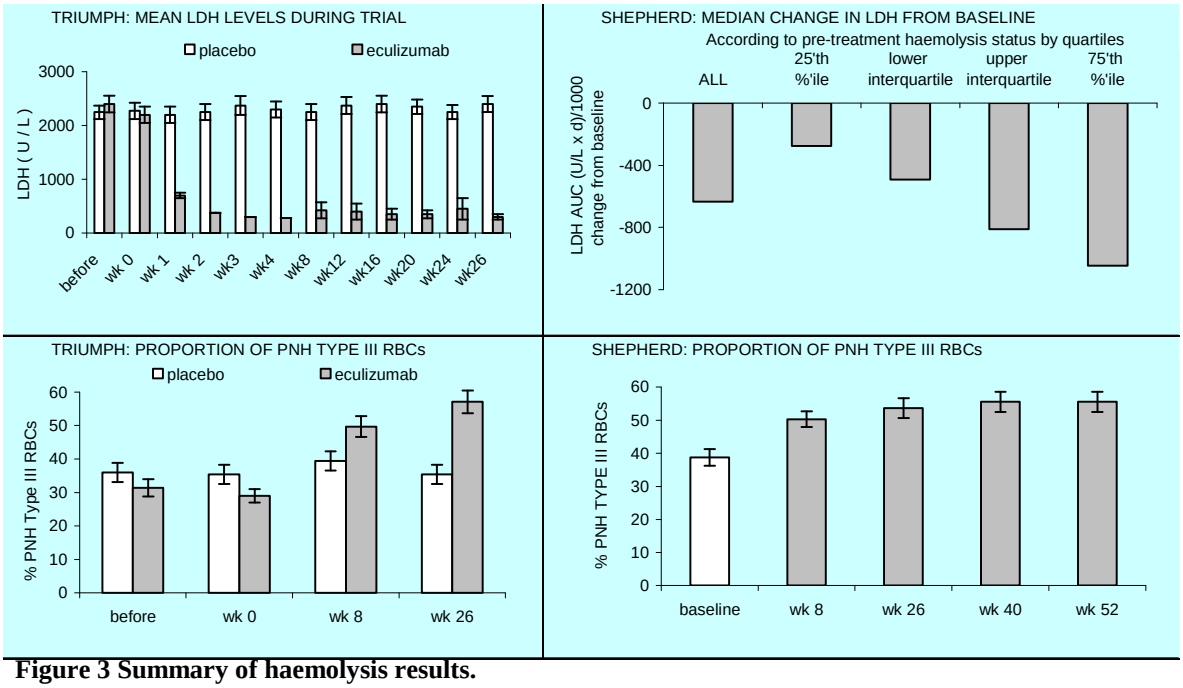

Figure 3 Summary of haemolysis results.

Error bars are SE. AUC = area under the curve. Participants were: TRIUMPH placebo=44, eculizumab=44; SHEPHERD N= 97. Results for the PILOT study are given in appendix 6.

Reduced haemolysis with eculizumab treatment in TRIUMPH was reflected in increased proportions of PNH Type III RBCs in circulation (Figure 3). PNH type III RBCs increased from 28.1 (± 2.0%) at baseline to 56.9 (± 3.6%) at end of study in the eculizumab group, but remained constant in the placebo group (35.7 ± 2.8% at baseline; 35.5 ± 2.8% at week 26) ($p < 0.001$ for eculizumab v placebo). Proportions of PNH type III granulocytes and monocytes did not change significantly.

Haemolysis results in the SHEPHERD study were broadly similar to those in TRIUMPH (Figure 3). LDH was reported as median change from baseline. Median LDH reduced by 630 U/L, the median LDH at baseline (week 0) was stated to be 2051 U/L. Mean LDH levels in SHEPHERD were reported separately in the EXTENSION study.[44] During the 52 weeks of treatment these results were similar to those for the eculizumab group in TRIUMPH. The proportion of PNH type III RBCs steadily increased from baseline during the SHEPHERD trial ($p < 0.001$ v baseline). The proportion achieved was similar to that in intervention arm of TRIUMPH (~55%).

Quality of life *(results summarised in Figure 4)*

Quality of life was measured using FACIT-Fatigue and EORTC QLC-C30 instruments. FACIT is a self report 13 item questionnaire, each item scored 0 to 4 giving a total range 0 – 52 with higher scores indicating less fatigue.[45] Change in FACIT score relative to baseline was reported for weeks 1 to 26 of the TRIUMPH RCT (Figure 4). Absolute scores were not reported. Mean changes from baseline were in direction of improvement for the eculizumab group but of worsening of fatigue for the placebo group.

The SHEPHERD study reported change from baseline in fatigue scores at multiple time points up to week 52. A trend for increase in scores and thus quality of life from baseline was evident from week one onwards (right hand panel Figure 4). At all time points there was a statistically significant improvement in FACIT score relative to baseline ($p < 0.001$). Changes were larger than in TRIUMPH. However, in TRIUMPH, patients received a transfusion just prior to baseline evaluation, whereas in SHEPHERD baseline evaluation did not necessarily closely follow a transfusion. Thus, there may have been more scope for improvement in fatigue with eculizumab

in SHEPHERD. This may also explain the deterioration in fatigue scores in the placebo group in TRIUMPH.

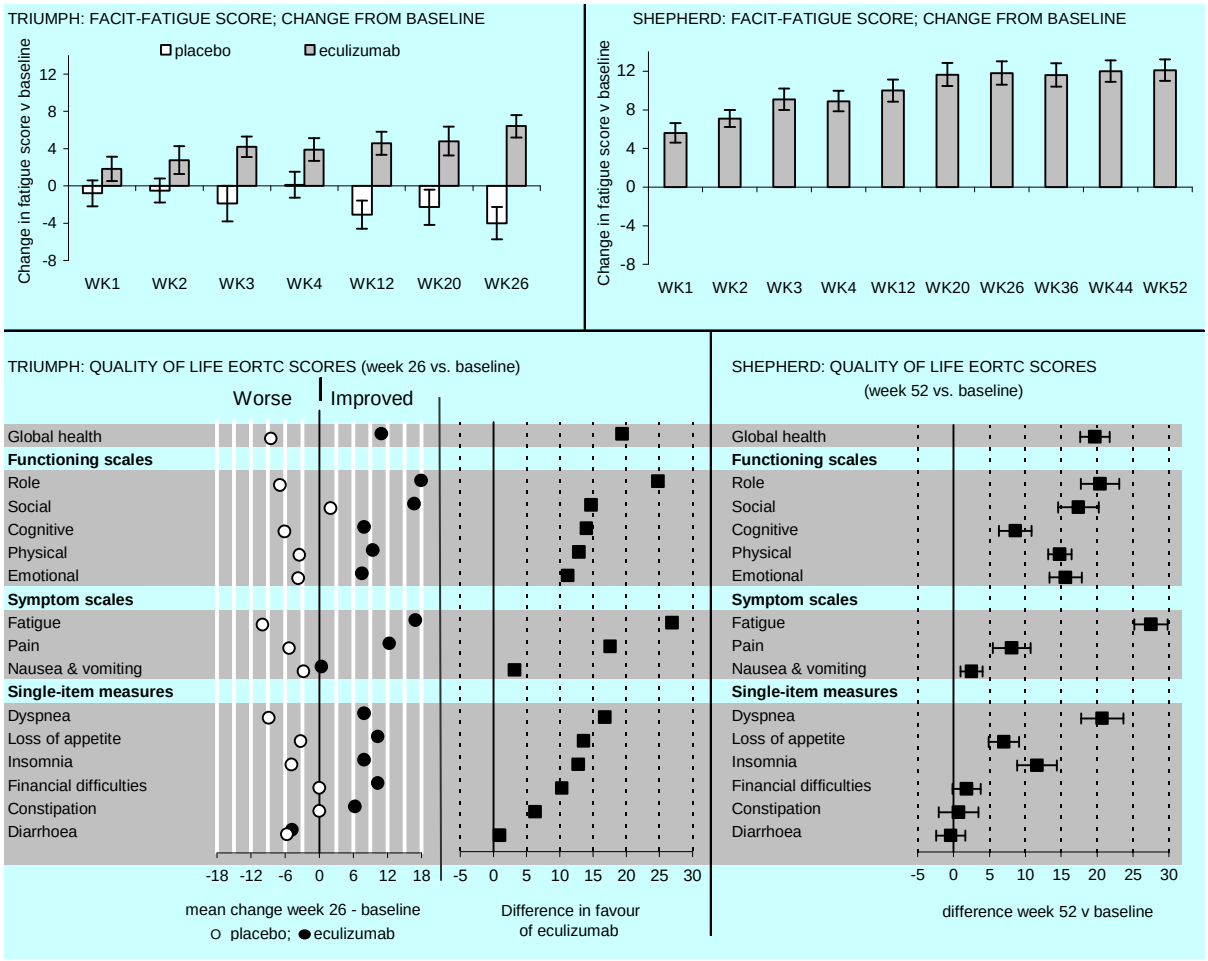

Figure 4 Summary of quality of life results

Error bars are SE. Participants were: TRIUMPH placebo=44, eculizumab=44; SHEPHERD N= 97. Where necessary EORTC scores were multiplied by -1 to make increase in score correlate with improvement.

In a submitted but as yet unpublished poster Hill et al 2008[46] have compared the improvement in FACIT scores observed for 165 TRIUMPH and SHEPHERD patients treated with eculizumab with changes reported in an open-label study of cancer patients (mixed diagnoses) treated with erythropoietin (EPO).[47] Increase in FACIT score with treatment was greater for eculizumab-treated PNH patients than for EPO-treated cancer patients (8.1 vs. 5.0). Furthermore whereas decreased fatigue with EPO was linked to an improvement in anaemia, with eculizumab fatigue diminished in patients with no improvement in anaemia as well as those with an improvement in anaemia. Since improvement in fatigue with eculizumab is associated with relatively rapid reduction in haemolysis and occurred independently of change in anaemia, eculizumab can apparently benefit a broader PNH patient population than those who realise improvement in anaemia.[46]

The EORTC QLQ-C30 instrument includes five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea & vomiting and pain) and a global health status/QOL scale. In addition, it contains six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).The TRIUMPH EORTC scores in all domains, other than diarrhoea, indicated improvement for the active treatment but worsening for the placebo group; the results (lower left panel Figure 4) indicated improvement in fatigue score for the eculizumab group. In SHEPHERD change in EORTC scores at week 52 relative to baseline were of similar magnitude to those in TRIUMPH and indicated quality of life improvements in all domains except diarrhoea, constipation and financial difficulties (right panel Figure 4). The improvement for the fatigue domain was maintained from week 1 through to 52 weeks ($p < 0.001$).

Safety results

Eculizumab was well tolerated for up to at least 52 weeks of treatment. There was one discontinuation in the 26 week TRIUMPH study that was unrelated to eculizumab, and there were no deaths. In SHEPHERD there was one withdrawal from treatment and 92 of 96 patients elected to continue treatment beyond 52 weeks. One death was recorded during the SHEPHERD trial and was attributed to thrombosis and judged unrelated to study drug; this patient had previously withdrawn from treatment due to disc prolapse also judged unrelated to study drug.

Other results about the safety of eculizumab were reported as numbers of serious adverse events (SAEs) and frequency of adverse events (AEs) that occurred in at least 10% of patients. During 26 weeks of eculizumab/placebo treatment in 87 patients in TRIUMPH, nine SAEs were recorded excluding exacerbations of PNH. Six occurred in the placebo group with one event in each of the following categories: central-line and urinary tract infection, upper respiratory tract infection, probable viral infection, neutropenia, cellulitis/folliculitis & neutropenia, anaemia & pyrexia. The 3 SAEs among eculizumab-treated-patients were recorded as renal colic, lumbar-or sacral-disk prolapse, and α-haemolytic streptococcal bacteraemia. Among AEs headache was the most frequent occurring in 44% of eculizumab patients and 27% of placebo patients. Other AEs were experienced at lower frequency in eculizumab

or placebo groups including nasopharyngitis (23%,18%), upper respiratory tract infection (14%,23%), back pain (19%,9%), nausea (16%,11%), cough (12%,9%), diarrhoea (9%,11%), arthralgia (7%,11%), abdominal pain (5%,11%), dizziness (5%,11%), vomiting (5%,11%), fatigue (12%,2%), viral infection (2%,11%). It is surprising that fatigue registered as an AE at higher frequency in the eculizumab than the placebo group. A transient low level immune response to eculizumab was observed in one patient.

During eculizumab treatment in SHEPHERD, 44 SAEs were observed of which 7 were considered possibly related to study drug, including pyrexia (2), headache, abdominal distension, viral infection, anxiety, and renal impairment. The nature of the other 37 SAEs was not reported. No SAEs were considered definitely or probably related to study drug.

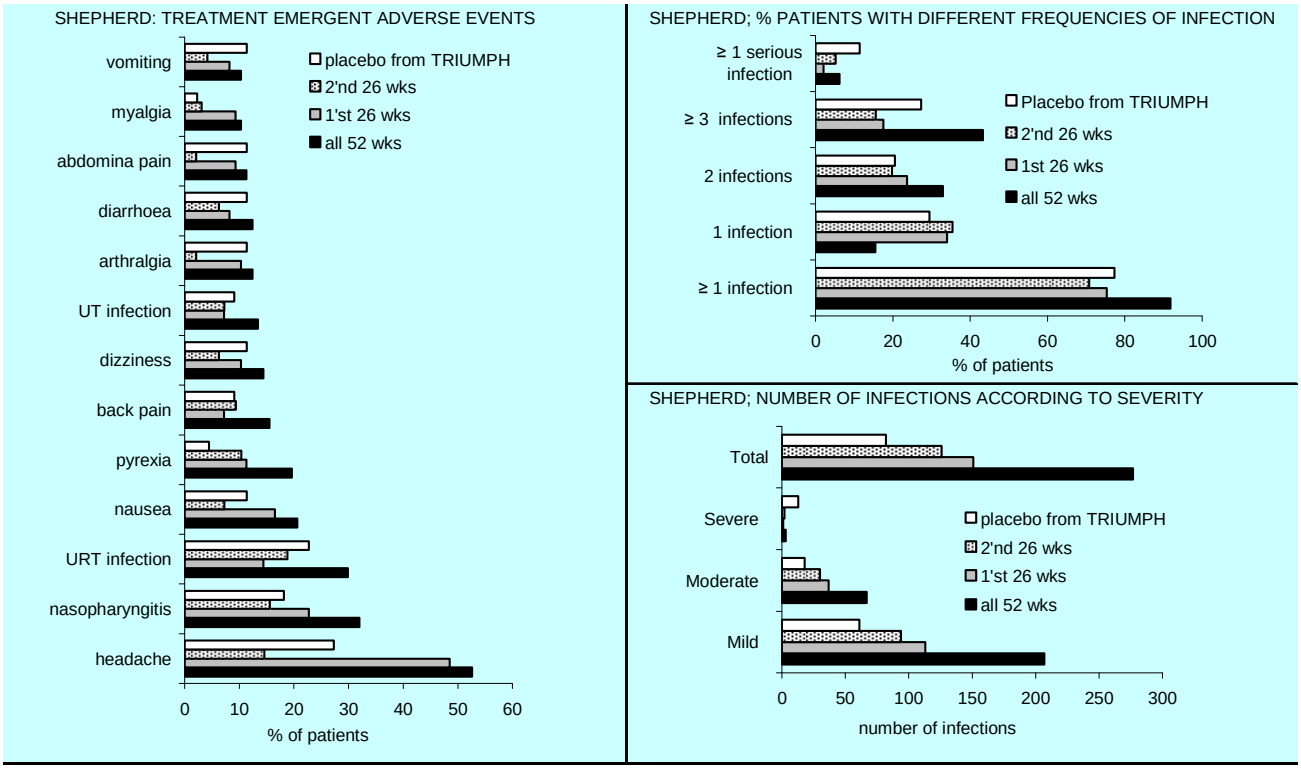

Figure 5 Adverse event and infection rates recorded in SHEPHERD and placebo group of TRIUMPH.

Treatment emergent AEs observed in more than 10% of patients are shown in Figure 5.

Most AEs (96.4%) were of mild to moderate intensity and most (74%) were considered unrelated to study drug. For most AEs listed the percentage of patients affected during each of the two 26 week periods was similar to that reported for the

placebo arm of the 26 week TRIUMPH RCT. It should be born in mind that there were differences between the populations enrolled for these two trials.

The most common AEs were headache, nasopharyngitis and upper respiratory tract infection. About half of patients experienced headache in the first 26 weeks, but only 15% in the second 26 weeks, a proportion less than that reported for the placebo arm of TRIUMPH. Most headaches occurred during the first two weeks of therapy. The authors suggest that treatment induces early rapid change in vascular NO levels that may lead to headache, followed by homoeostatic return of steady state NO levels and associated reduction in headache.

Most patients (92%) experienced at least one infection; only 1.1% of infections were classified as severe. The proportion of patients with various frequencies of infections was similar to that for the TRIUMPH placebo group (Figure 5). The absolute number of infections of various severities was greater for the first and second 26 week periods of SHEPHERD than for the TRIUMPH placebo arm, however the latter had only half as many patients so that infections/patient/26 weeks are likely to be similar. Two patients developed low titre immunogenecity to eculizumab. Detection is dependent on assay technique and in response to the EMEA the manufacturer has committed to develop appropriate detection methods.[14]

The summary of product characteristics[15] notes there have been 3 reported cases of meningococcal infection in patients treated with eculizumab: two in vaccinated individuals and one in an unvaccinated patient.

Thromboembolism results

Patients from the PILOT, TRIUMPH, and SHEPHERD trials were analysed in the EXTENSION study.[44] The incidence of thrombosis during treatment was collected prospectively according to set criteria and compared with pre-treatment incidence determined by retrospective analysis of medical notes according to the same criteria. Thromboembolism rate decreases with eculizumab treatment. During treatment the incidence was 1.07/100 patient years (py); there were three events amongst 195 patients who accumulated 281 py of observation. There were 1683.4 py of pre-treatment observation for the same 195 patients during which 124 events were

recorded giving a rate of 7.37 events/100 py. and a relative rate of 6.9 (7.37/1.07). The comparison of rates before-treatment vs. during treatment was statistically significant (p<0.001). The rate during treatment was based on one sixth the observation time for the pre-treatment rate and only 3 events were observed making the estimate susceptible to the influence of chance. Although different temporal relationships of event ascertainment may compromise the accuracy of the relative rate estimate the difference in rates (before treatment vs. during treatment) is so great it is difficult to doubt a beneficial effect of treatment. The pre-treatment rate for 97 SHEPHERD patients (12.67/100 py) was more than double that for the 87 TRIUMPH patients (2.34 for placebo group and 5.18 for intervention group). Therefore for the combined rate of 7.37/100 py to apply for patients qualifying for eculizumab treatment it would be necessary for the qualifying population to consist of a similar ratio of TRIUMPH-like and SHEPHERD-like patients as in the trials.

Renal function results

A *post hoc* retrospective analyses of chronic kidney disease (CKD) status and incidence of major clinical kidney (MCK) events in the EXTENSION study has been undertaken.[44] Table 5 lists CKD status at initial screening (pre-treatment).

Table 5 Chronic kidney disease (CKD) in PNH patients at screening (N=193)

CKD STAGE	N	(%)
STAGE 5 (GFR < 15 mL/min/1.73 m^2)	3	(1.5%)
STAGE 4 (GFR 15 - 30 mL/min/1.73 m^2)	7	(3.6%)
STAGE 3 (GFR 30 - 60 mL/min/1.73 m^2)	30	(15.4%)
STAGE 2 (GFR 60 – 90 mL/min/1.73 m^2) with evidence of kidney damage	48	(24.6%)
STAGE 1 (GFR > 90 mL/min/1.73 m^2) with evidence of kidney damage	36	(18.5%)
NO CKD	69	(36.4%)
Median GFR (range) = 80 (63 – 97) mL/min/1.73 m^2 ; GFR = glomerular filtration rate. Assessment of CKD status depended on a measure of glomerular filtration rate (GFR) used as an indicator of renal function. GFR was estimated indirectly according to National Kidney Foundation criteria[48] using serum creatinine values and an equation taking factors of age, sex, race and calibration for serum creatinine into account.		

In Figure 6 the reported changes in CKD status are illustrated. Amongst TRIUMPH patients (the upper panel Figure 6) most (66% eculizumab and 69% placebo) had not changed CKD status by end of the randomised phase. Relative to CKD status at baseline 29% (12/41) of patients in the eculizumab group and 17% (7/42) in the placebo group had improved (white columns) while for patients with CKD at baseline 5% (2/41) in eculizumab and 14% (6/42) in placebo groups had worsened (shaded, downward columns). None of the eculizumab group without CKD at baseline worsened while 3/19 (15%) without CKD in the placebo group worsened. Eculizumab patients were more likely to change status (improve or worsen) than placebo-treated

patients (p = 0.04) and were 6 times more likely to improve (12/41) than to worsen (2/41). Placebo patients were equally likely to improve (7/42) as worsen (6/42). A greater proportion of patients with lower grade CKD (stages 1 and 2) at baseline exhibited an improvement by 26 weeks (64.7% eculizumab, 35.7% placebo) than did the higher grade stage 3-5 patients.

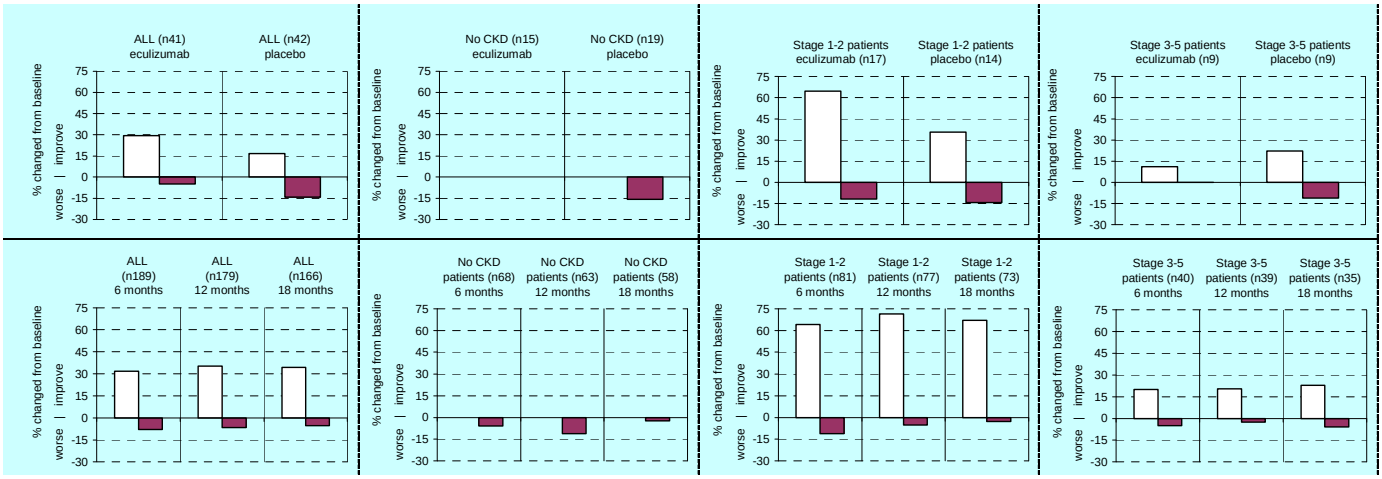

Figure 6 Proportions of patients with improved or worsened CKD score relative to baseline

Proportions of patients showing improvement in CKD are represented by a positive % (white columns), proportion of patients exhibiting a worsening in CKD are represented by a negative % (shaded columns). Upper panel: observations made in the 26 week TRIUMPH RCT. Lower panel refers to observations in the open label EXTENSION study.

Relative to baseline most participants in the EXTENSION study had unchanged CKD status at 6, 12 and 18 months follow up (60%, 58% and 60% respectively). Of those patients whose CKD status changed (Figure 6 lower panel) far more improved than worsened; the proportion improved was stable across 6 to 18 months; participants with stages 1 – 2 CKD at baseline were more likely to improve than those at stage 3 – 5 at baseline. The results for placebo-group patients in TRIUMPH show that improvement is possible for a few patients independent of eculizumab treatment.

MCK events were defined as events with severe renal damage (including acute or chronic renal failure), renal insufficiency, renal impairment, dialysis and procedures, nephrotoxicity, scarred or necrotic kidney, pyelonephritis, glomerulopathy or stage 3 – 5 CKD. MCK events were determined by case report review. Kaplan-Meier analysis indicated the median time from diagnosis to a MCK event was about 26.5 years (data read from graph). By 37.5 years 83% had experienced a MCK event.[36] No results were presented with regard to the efficacy of eculizumab treatment for MCK.

Summary of evidence of clinical effectiveness

- Effectiveness evidence came from a small pilot study (11 patients) and multi-centre industry sponsored studies comprising a double blind good quality RCT of 6 months duration with 87 patients (TRIUMPH), a 12 month uncontrolled trial with 97 patients (SHEPHERD), and an ongoing EXTENSION study with patients from the previous trials. All patients had a history of transfusions, those in SHEPHERD less so than in TRIUMPH.
- Eculizumab reduced transfusion requirements and anaemia. In TRIUMPH 51% of the eculizumab group but 0% of the placebo group remained independent of packed red blood cell transfusion and mean units-transfused/26 weeks pre-treatment was reduced by ~70% with eculizumab but remained unchanged with placebo. In SHEPHERD units transfused reduced to a mean of 5.9 units during 52 weeks of treatment from 12.3 units in the 52 weeks pre-trial. Mean haemoglobin at 26 weeks was improved in the eculizumab arm of the RCT but deteriorated with placebo. In SHEPHERD mean haemoglobin was increased at 52 weeks compared to baseline.
- Eculizumab reduced haemolysis. In the RCT eculizumab but not placebo greatly reduced mean LDH levels and increased the proportion of circulating Type III RBCs. In SHEPHERD treatment was associated with a similar reduction in LDH and increase in Type III RBCs relative to baseline.
- Compliance was good. In the RCT, the most common adverse events more frequent in treatment relative to placebo were headache, upper respiratory tract infection and viral infection. No patient withdrew due to side effects. In SHEPHERD one patient died due to thrombosis judged not related to study drug; of 96 patients 92 elected to continue treatment beyond 1 year.

- In SHEPHERD there were 44 serious adverse events with 7 considered possibly related to study drug (pyrexia (2), headache, abdominal distension, viral infection, anxiety and renal impairment). No serious adverse events were judged probably or definitely related to eculizumab. In the last 26 weeks of SHEPHERD, with the exception of pyrexia, most adverse events occurred at rates comparable to the placebo arm in TRIUMPH. In the first 26 weeks headache occurred at high frequency, mostly early after the start of treatment; the rate had subsided below that of the TRIUMPH placebo arm by the second 26 weeks. The numbers and severity of infections in SHEPHERD were similar to those in the placebo arm of TRIUMPH.
- Eculizumab improved patient's quality of life, especially with regard to fatigue. Patient scores in the FACIT-fatigue questionnaire steadily improved during treatment. Diminished fatigue was experienced by patients whether their anaemia improved or not. EORTC quality of life scores also improved relative to baseline.
- The EXTENSION study provided evidence that eculizumab reduced thrombosis rates about 7 fold and *post hoc* analyses indicated eculizumab improved or prevented worsening of renal function in some patients.
- CONCLUSION: Eculizumab is highly effective at reducing haemolysis with consequent reduced demand for transfusions and improvement in anaemia and quality of life, especially with respect to fatigue. It considerably reduces the rate of thrombosis and therefore likely improves life expectancy, but good estimates of effect sizes await further investigation. It is well tolerated but the short-term nature of observations of potential side effects necessitates continued vigilance.

4.4 Systematic review of cost-effectiveness of eculizumab

No published or unpublished economic studies were identified.

Barriers to modelling cost-effectiveness of eculizumab vs. standard care

The major parameters of cost and benefit required to build a decision analytical model for the cost-effectiveness of eculizumab vs. standard care (SC) can be identified. Unfortunately lack of reliable quantitative information about these parameters means implementation of a fully informed model for estimation of cost-effectiveness in terms of £/QALY is impractical at this time.

One overriding problem is uncertainty about the PNH population that would be eligible for treatment; this could be all PNH patients or, according to expert clinical opinion, a subpopulation of frankly haemolytic patients, or patients with a history of transfusion and pronounced haemolysis. Most available information about prognosis in SC comes from studies examining all PNH patients, whereas clinical trial data about effectiveness of eculizumab comes exclusively from studies conducted on patients with a history of transfusion. No clear criteria have been developed that define a patient with a history of transfusion or one with frank haemolysis. Furthermore, the two clinical trials (TRIUMPH and SHEPHERD) investigated populations with different transfusion histories and different pre-treatment thrombosis rates and it is unclear what proportion of all patients that might be eligible for treatment these trial populations might represent.

4.4.1 Preliminary analyses of cost-effectiveness

Due to the above-mentioned constraints, only preliminary analyses of cost-effectiveness of eculizumab were carried out for this report. Three analyses were undertaken to determine the incremental cost-effectiveness ratio (ICER): i) per stabilisation of haemoglobin and per stabilisation of LDH; ii) as cost/life year gained (LYG) for a variety of costs of SC and cost of SC avoided by treatment with eculizumab; iii) as cost/LYG for averting thrombosis related mortality with eculizumab. These are outlined below.

Analysis I: *Cost-effectiveness per stabilisation of haemoglobin or LDH*

The main clinical outcomes of eculizumab from the RCT include (a) 49% (21/43) of patients in the eculizumab group maintain haemoglobin level above the pre-specified set points compared to 0% (0/44) in the placebo group and (b) 37% (15/41) had a LDH level within the normal range compared to 0% in the placebo group. With the recommended dose regimen, the first year of treatment costs £252,000 and a subsequent year costs £245,700. The RCT only lasted 26 weeks. Therefore the first half-year of treatment would cost £126,000. These give an incremental cost-effectiveness ratio of £257,142 (126000/0.49) per stabilisation of haemoglobin levels gained, and an incremental cost-effectiveness ratio of £340,541 (126,000/0.37) per normal range of LDH level achieved. However, considerable clinical benefit is likely to accompany greatly reduced LDH levels that do not necessarily completely normalise. In the RCT 95.1% and 0% of eculizumab and placebo patients respectively achieved LDH levels of less than 2x the upper normal limit. For this end point the ICER calculates to £132,492 per patient achieving the end point.

Although estimation of these types of ICERs for these outcomes is narrow in scope these analyses were based on the available clinical effectiveness evidence from the RCT.

Analysis II: *Cost-effectiveness for a variety of standard care costs, savings and survival rates*

It is clear that PNH is life threatening and that the major potential benefit of eculizumab treatment is likely to be an extension of life expectancy. There is no direct evidence about the impact of eculizumab on mortality but it can be inferred from estimates about the reduction in rates of thrombosis that it could be substantial. Natural history studies of European PNH cohorts indicated that, on average, over 25 years PNH claimed between about 10.2[21] and 4.5[32] years of life relative to the general population. We assume that survival in SC of patients eligible for eculizumab treatment lies somewhere between the extremes reported for the European cohorts which consist of all diagnosed patients.[21 32] Assuming a perfect drug scenario, in which eculizumab treatment returns survival to that of the general population, then over a 25 year time horizon the corresponding cost of eculizumab

drug provision/life year gained (LYG) is between £0.6M and £1M (discounting both cost and LYG at 3.5%, and setting annual eculizumab cost £245,700/patient).

To estimate an ICER for eculizumab we need to know the cost of SC and savings from SC avoided by treatment with eculizumab (e.g. reduced requirement for transfusions, treatment for non-fatal thromboses, treatment for chronic kidney disease). There are no published estimates for these parameters. Therefore we investigated the influence of SC costs and of savings in these by using eculizumab by setting annual cost of SC at between £1,000 and £100,000 per patient and savings at 50% and 90%. PNH patient survival in SC was varied to correspond to that reported by Hillmen 1995,[21] Socie 1996[22] and Latour 2006[32] (median survival 10.2, 16.1, and 27.4 years after diagnosis; life years saved over 25 year span 10.2, 7.2 and 4.5 years respectively). Costs and benefits were discounted at 3.5%. Results are shown in Figure 7.

ICERs range between £0.5M and £1.4M/LYG. The ICER is more sensitive to cost of SC when LYG are small (4.5 years) and savings high (90%). If SC costs are increased indefinitely beyond £100K then, with 90% SC cost saved, the intervention will eventually become cost-saving. This does not happen until annual SC cost climbs to extremely high values.

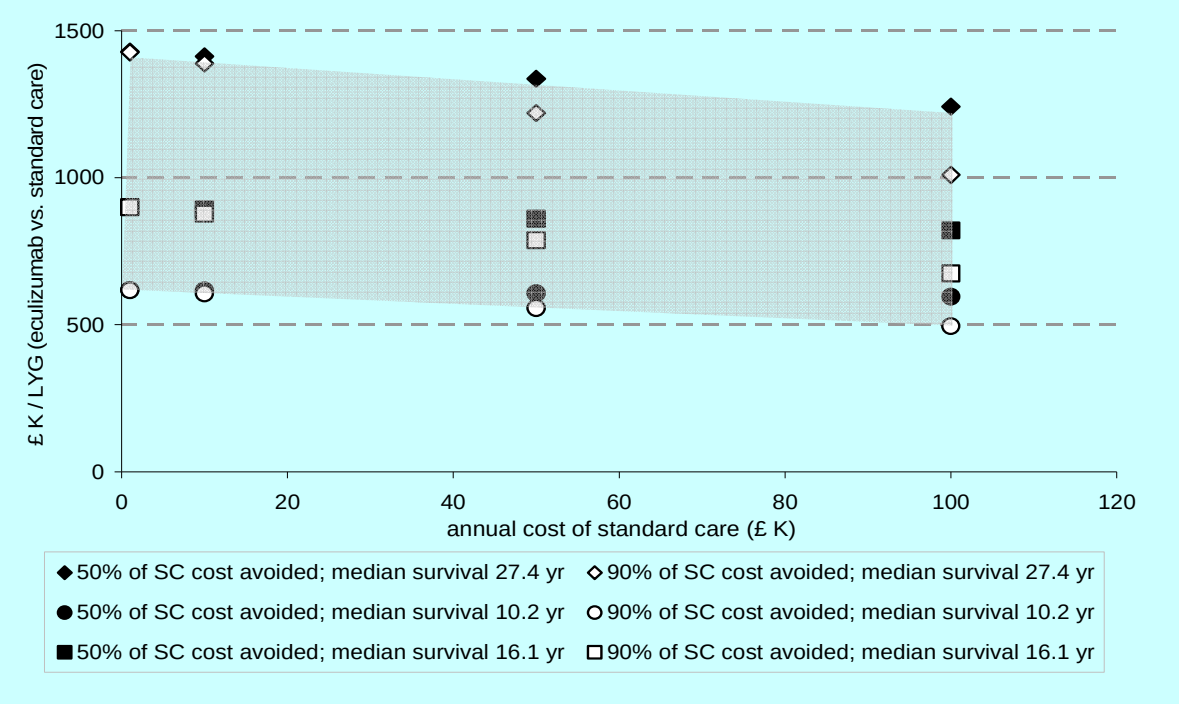

Figure 7 ICER values for eculizumab v. standard care (refer to text and Appendix 8 for details).

Analysis III: *Cost-effectiveness for averted thrombosis-related mortality*

When we integrate information obtained from clinical effectiveness studies and prognosis studies (without use of eculizumab), it becomes possible to derive clinical effectiveness in terms of risk reduction of thrombosis, and consequent increase of life expectancy due to the intervention. A simple model structure is shown in Figure 8.

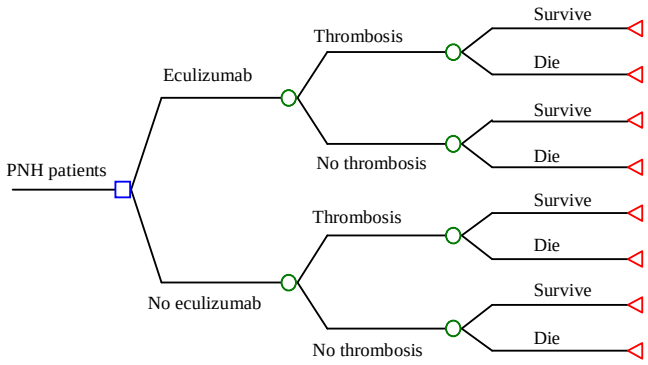

Figure 8 A simple model structure for eculizumab versus no eculizumab treatment

The model follows PNH patients (either PNH patients with a history of transfusions or, for extreme sensitivity analysis, all diagnosed PNH patients) who are divided into two groups: those with eculizumab and those with no eculizumab. Patients in either group may develop thrombosis, some of whom will die. A time horizon of 10-15 years (based on reported median survival times) is used. Cost-effectiveness is measured in terms of £/LYG. A discounting rate of 3.5% is applied to both cost and LYG. The costs of standard care are not considered since differential data about costs with and without thrombosis are unavailable.

For a mixed population of PNH patients with a history of transfusions, the thrombosis rates were estimated to be 1.07 per 100 py for patients treated with eculizumab and 7.37 per 100 py for pre-eculizumab PNH patients.[44] The thrombosis rate for all diagnosed PNH patients was estimated in this report to be 4.22 per 100 patient years for patients without use of eculizumab. The thrombosis rate for all PNH patients treated with eculizumab was taken to be 0.61 per 100 py (the same relative risk as that for PNH patients with a history of transfusions (1.07/7.37 = 0.15) was applied). In both populations the mortality rates of 52% (Appendix 9) for patients with thrombosis, and 15% (Appendix 10) for patients without thrombosis were used.

Figure 9 shows the ICERs for eculizumab use compared to no use for PNH patients with a transfusion history and for all diagnosed PNH patients. These are also summarised in Table 6 and Table 7. The results show that the ICER for PNH patients with a history of transfusions varies from £1.2M/LYG to £1.4M/LYG for different median survival years. The ICER for all diagnosed PNH patients, used to determine the ICER upper limit, varied from £2.8M/LYG to £3.2M/LYG for different median years survival.

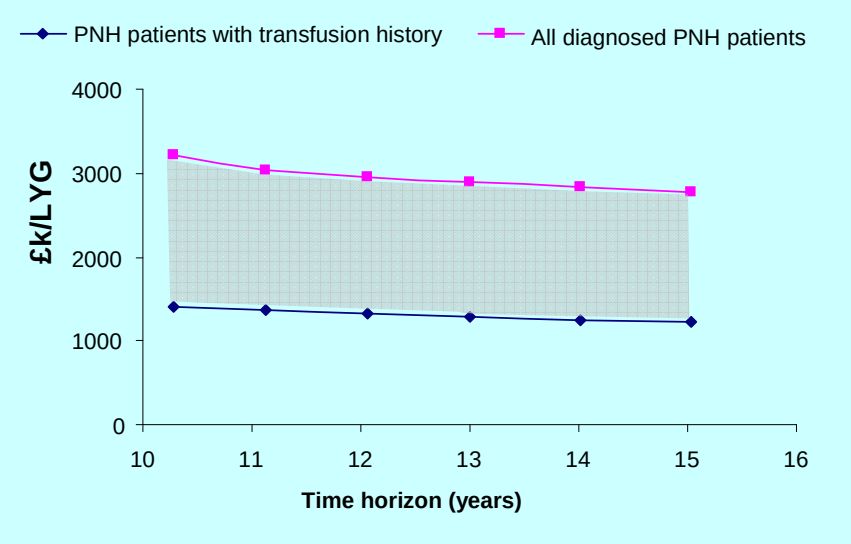

Figure 9 Cost-effectiveness (£K/LYG, eculizumab v standard care) according to time horizon

Table 6 Cost-effectiveness (£/LYG) v. time horizon: PNH patients with a history of transfusions

Median survival year	Cost (Ecu.) (£K)	Cost (No ecu.) (£K)	Cost difference (£K)	LYG (Ecu.)	LYG (No ecu.)	LYG	ICER (£K/LYG)
10	2199	0	2199	8.8	7.24	1.56	1,409
11	2347	0	2347	9.39	7.67	1.72	1,364
12	2490	0	2490	9.96	8.08	1.88	1,324
13	2655	0	2655	10.62	8.56	2.06	1,289
14	2815	0	2815	11.26	9.01	2.25	1,251
15	2968	0	2968	11.87	9.45	2.42	1,226
Thrombosis rate of 7.37% per year without Eculizumab and 1.07% per year with Eculizumab.							

Table 7 Cost-effectiveness (£/LYG) v. time horizon: all diagnosed PNH patients

Median survival year	Cost (Ecu.) (£K)	Cost (No ecu.) (£K)	Cost difference (£K)	LYG (Ecu.)	LYG (No ecu.)	LYG	ICER (£K/LYG)
10	2248	0	2248	8.99	8.29	0.70	3,211
11	2401	0	2401	9.61	8.82	0.79	3,039
12	2549	0	2549	10.2	9.34	0.86	2,964
13	2721	0	2721	10.89	9.95	0.94	2,895
14	2886	0	2886	11.55	10.53	1.02	2,829
15	3044	0	3044	12.18	11.08	1.10	2,768
Thrombosis rate of 4.22% per year without Eculizumab and 0.61% per year with Eculizumab.							

Summary of economic analysis

- Literature searches failed to identify any economic analyses of PNH treatments.
- Lack of reliable quantitative information means implementation of a fully informed model for estimation of cost-effectiveness in terms of £/QALY is impractical at this time.
- We conducted three preliminary economic evaluations for the use of eculizumab vs. standard care:

  I] The first analysis, based on RCT evidence, showed that the incremental cost-effectiveness ratio between use of eculizumab and no use of eculizumab is ~£257K per patient gained with stabilised haemoglobin, ~£341K per patient gained with normalised LDH level, and ~£132K per patient with LDH level less than twice the upper normal limit.

  II] A second analysis showed that the incremental cost-effectiveness ratio varied from about £0.5M to £1.4M/LYG under the assumptions of a “perfect drug” effect on survival (median survival of PNH patients 10.2, 16.1 or 27.4 years returned to normal), annual standard care (SC) cost up to £100K per patient, and 90% of SC cost saved by use of eculizumab.

  III] A third analysis based on thrombosis rates and mortality rates from thrombosis showed that the ICER for PNH patients with a history of transfusions varied from £1.2M/LYG to £1.4M/LYG depending on the time horizon (10 to 15 years). The ICER for all diagnosed PNH patient, used to define an upper limit, varied from £2.8M/LYG to £3.2M/LYG depending on the time horizon (10 to 15 years).

5. FACTORS RELEVANT TO NHS

According to prevalence data we would expect about 870 PNH patients in England and Wales (population 55M), and about 87 in the West Midlands (population 5.5M). If a 25% were judged eligible for treatment with eculizumab then the annual cost to the NHS West Midlands for provision of the drug would be about £5.1M in year one. For England and Wales provision cost would be about £51M. This cost assumes home delivery service to patients would be provided free by the manufacturer. Expert clinical opinion considered that in the UK eculizumab would be indicated only for clearly haemolytic PNH (2.4 patients per million population); on this basis 13 patients would be treated in the West Midlands representing 15% of the 87 patients expected on the basis of reported prevalence; first year drug provision would then cost ~£3.3M (and £33M if applied to England and Wales).

The cost to the NHS of drug provision would be offset by savings due to reduced costs associated with SC. Such savings might be associated with a reduction in transfusion rates, a reduction in incidence of non-fatal thromboses and their associated costs of treatment, and reduction in chronic kidney disease. The magnitude of these saving is difficult to estimate. To gain some idea of budget impact over the next 5 to 10 years from uptake of eculizumab in the West Midlands we adopted the following assumptions:

- There are 87 patients with PNH (prevalence 1.59/100,000[19]).
- 16% (14 patients), 25% (22 patients) or 33% (28 patients) of current patients qualify to receive eculizumab at standard dose.[49]
- Treatment lasts throughout the budget period (100% compliance and survival based on trial data about withdrawals and risk reduction of thrombosis).
- Of patients not offered treatment 2% per year would become eligible and receive treatment (based on 20.5 years to first thrombosis and assuming a linear relationship[22]).
- 7 new diagnoses of PNH are made per year, starting in year 2.[19]
- Newly diagnosed patients are subject to the same assumptions as current patients.
- Annual cost of eculizumab provision is £245,700 per patient.

- Savings per year over 10 years varied from ~£1K (equivalent to ~2 transfusions avoided per patient per year), to far greater savings of £10K, £100K or £200K.
- No discounting of acquisition costs or savings costs or of benefits.

Figure 10 shows the budget impact under these assumptions. With between 16% and 33% of patients treated immediately and between £1K and £10K savings from avoided standard care expenditure the annual cost in year one would be between £3.3M and £7.0M, and at 10 years ranges between about £9.5M and £15.3M. If greater savings of between £100K and £200K are made from standard care treatments avoided then at 10 years annual cost ranges between about £1.8M and £9.1M.

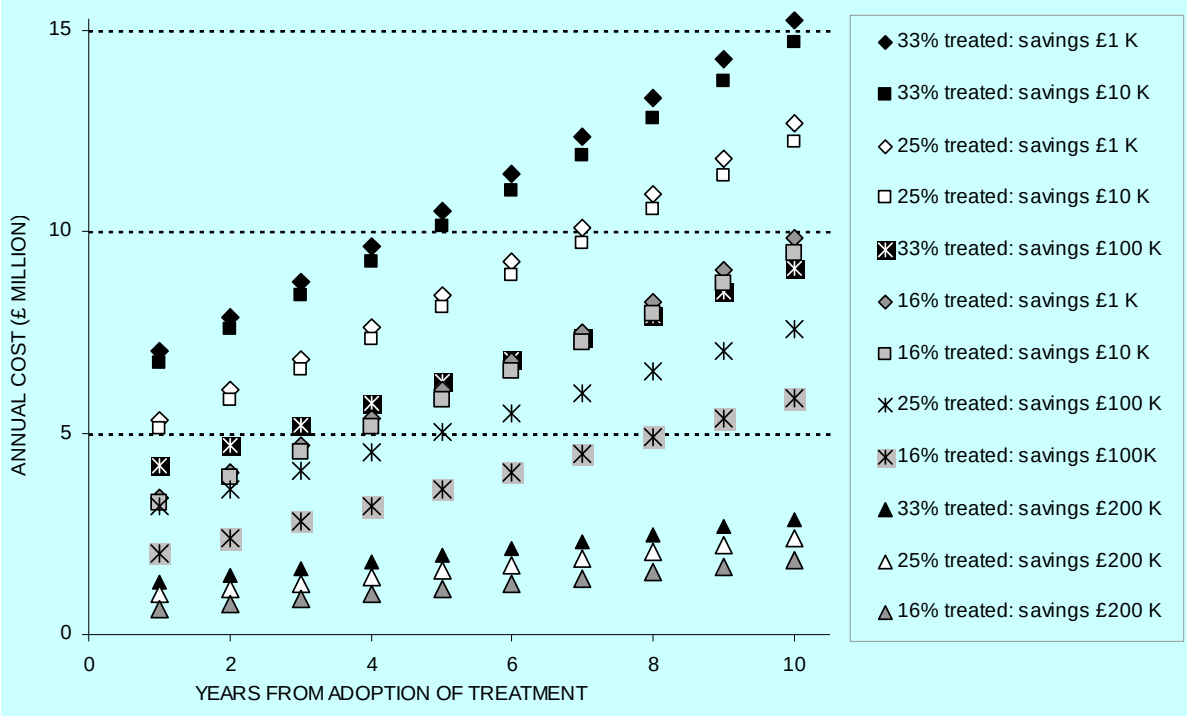

Figure 10 Annual cost of adoption of eculizumab in the West Midlands.

Assumptions include: current number of patients is 87; 7 new diagnoses are added annually; 16%, 25% or 33% become immediately eligible for treatment (starting year 2 for newly diagnosed patients); 2% of untreated patients become eligible for treatment annually. Savings from standard care set at £1K, £10K, £100K and £200K.

The budget analysis for the West Midlands requires the same success rate in diagnosing PNH patients as that underlying the prevalence study of Hill et al.[19]

The sample size in studies of eculizumab with extended observation of about 200 patients favourably compares with the evidence base underpinning the clinical effectiveness of several other ultra-orphan drugs. The cost of treatment is of the

same order of magnitude. Examples include: imatinib for gastrointestinal stromal tumours (no RCT; annual treatment cost ~£24K), β–glucocerobrosidase for Gaucher's disease (one RCT in three arms, total patients 29; annual treatment cost ~£325K); α-galactosidase for Fabry's disease (three small RCTs, total patients 99; annual treatment cost ~£120K) and α–L-iduronidase for mucoplysaccharidosis type 1 (no RCT, only one controlled study; annual treatment cost ~£335K, or £96K for a 20 kg child).[50-52]

A recent article lists 18 orphan medicines approved in 2006 for marketing in the EU.[53] Work by The National Horizon Scanning Centre indicates that many more orphan and ultra-orphan drugs are likely to receive marketing approval in the next 5 to 10 years.[54] The sustainability of funding policies in the face of increasing approvals by licensing authorities for very expensive orphan drugs has been debated as although the budget impact of drug provision for individual rare diseases is relatively minor, the future cumulative total impact could be considerable.[55,56]

This could lead to questions about equal access to treatments. It raises issues for decision makers, as some patients will be treated with drugs already commissioned, because these were early in the queue for marketing approval, while patients eligible for treatment with drugs that are later in the queue, such as eculizumab, still need to be considered equally but in the face of mounting budget constraints. These constraints may in part result from the steadily increasing number of licensed orphan drugs. This is currently an area of debate within health commissioning regionally, nationally and internationally.

6. DISCUSSION

6.1 Main results

The estimated incidence of PNH was 0.13/100,000/year, which indicates that about 7 new PNH cases will be diagnosed per year in the West. The 15 year prevalence was estimated to be 1.59/100,000. This corresponds to about 87 PNH patients in the West Midlands.

The identified studies related to the natural history and prognosis of PNH suggests that PNH may occur at any age from infancy through to old age, with a median of 30 to 40 years. The serious complications of PNH include anaemia, thrombosis, haemorrhage, acute myeloid leukaemia, impaired kidney function, bone marrow failure, and death. Most studies did not observe clinical remission for any PNH patient. However two studies reported a long term clinical remission for 15 to 25% of PNH patients.

Data summarised from three studies which had similar median follow up periods (6 to 7 years) provided an estimated thrombosis rate of 26%, with a median time to thrombosis of 2 to 5 years from diagnosis. This corresponds to 4.22 events per 100 patient years if a linear trend is assumed. For accurate estimation of the thrombosis rate, survival analysis should be carried out for all identified studies. This could not be undertaken due to the absence of appropriate published data.

Median survival after diagnosis for European cohorts varied between about 10 and 27 years, and appeared superior the more recent the cohort. For a UK cohort followed from 1970 to 1994 median survival after diagnosis was 10 years; loss of life years from PNH averaged about 10.2 years across a 25 year time span.

Prognostic factors associated with the progression to death and severe diseases include thrombosis, pancytopenia, myelodysplasia, acute leukaemia, advance age, severe leukopenia, severe infection, and renal failure. Thrombosis is the major identified cause of death. The mortality rates were estimated to be 52% for patients with thrombosis, and 15% for patients without thrombosis, respectively. It is

reasonable to assume that a treatment with a reduction of thrombosis could lead to a reduction of mortality.

The good quality RCT suggested that Eculizumab not only reduced haemolysis, anaemia and transfusion dependence, but also improved quality of life especially with regard to fatigue. At end of follow up 51% of the eculizumab group but none of the placebo group remained independent of packed red blood cell transfusion. Units-transfused before treatment was reduced by ~ 70% during eculizumab treatment but remained unchanged with placebo. Eculizumab greatly reduced mean LDH levels indicating considerable diminution in haemolysis, but LDH levels were unaffected by placebo. Compliance was good, SAEs were infrequent, and no patient withdrew from active intervention due to side effects. The most common adverse events occurring more frequently in treatment relative to placebo were headache, upper respiratory tract infection and viral infection. Open label and extension studies supported the RCT findings and provided evidence that eculizumab considerably reduced the probability of thrombosis.

One overriding problem is uncertainty about the PNH population that would be eligible for treatment; this could be all PNH patients or a subpopulation of frankly haemolytic patients or PNH patients with a history of transfusions, or only patients more severely affected and with considerable transfusion requirements. Available information about prognosis in SC comes from studies examining all PNH patients, whereas clinical trial data about effectiveness of eculizumab comes exclusively from studies conducted with PNH patients with a history of transfusions. Furthermore, the two clinical trials (TRIUMPH and SHEPHERD) investigated populations of quite different transfusion history and it is unclear what proportion of all PNH patients with a history of transfusions, or of all PNH patients, these trial populations might represent. A clear treatment definition is ideally required.

No economic evaluation studies were found. It was impractical to carry out a comprehensive economic evaluation for the use of eculizumab against standard care. We therefore conducted three preliminary economic evaluations for the use of eculizumab based on the available evidence and wide ranging assumptions. The results showed that the incremental cost-effectiveness ratio between use of

eculizumab and no use of eculizumab is ~£257,100 per patient gained with stabilised haemoglobin, ~£340,500 per patient gained with normalised LDH level, and ~£132,500 per patient with LDH level less than twice the upper normal limit. This analysis was simply based on the cost of eculizumab and the effect size of eculizumab obtained from the RCT. Under the assumptions of a "perfect drug" effect on survival, annual standard care cost up to £100,000 per patient, and up to 90% of SC cost saved by use of eculizumab, the incremental cost-effectiveness ratio varied from about £0.5M to £1.4M/LYG depending on estimates of life years saved by treatment ranging from 4.5 years to 10 years over a 25 year time span. Further analysis based on thrombosis rates for PNH patients with a history of transfusions (1.07% per year with eculizumab treatment and 7.37% without) or for all diagnosed PNH patients (0.61% per year with eculizumab treatment and 4.22% without) showed that the ICERs varied from £1.2M/LYG to £1.4M/LYG and £2.8M/LYG to £3.2M/LYG depending on time horizon (range 10 to 15 years).

Estimation of cost-effectiveness in terms of £/quality adjusted life year (QALY) requires attaching utility values to the QOL of patients in SC and in eculizumab treatment. Utility measures for PNH patients are lacking and utility gain from eculizumab treatment unavailable. It has been suggested that reduced QOL from chronic haemolysis and associated fatigue and anaemia in PNH may be comparable with that of cancer patients with anaemia.[4,57] Utility values for various levels of anaemia in cancer patients have been published; a difference in haemoglobin level of 8.9 compared to 10.1 (as seen between placebo and eculizumab groups at end of the TRIUMPH RCT) was associated with a modest utility difference of approximately 0.15.[9] However it has been argued that in PNH haemolysis has the main detrimental influence on QOL so that blocking haemolysis with eculizumab could deliver greater utility gain than that estimated from an improvement in anaemia. The results in the SHEPHERD trial lend support in that improvements from baseline in FACIT fatigue score were larger for those patients with the most haemolysis at baseline. Further support comes from the recently submitted poster comparing FACIT score changes in eculizumab-treated PNH patients and EPO-treated cancer patients (see section 4.3.2 *Quality of life*)

Some deficiencies in data, common for diseases like PNH because of their very low prevalence, may be addressed in the future by patient data registries such as that recently set up by Alexion Pharmaceuticals.[58] Further research should be directed toward the following:

- Long-term follow up of cohorts of patients to investigate clinical remission rate of PNH
- Survival based analysis of thrombosis using individual patient data from previous and future studies.
- Follow-up studies to delineate disease progression in patients qualifying for and receiving various interventions including eculizumab.
- Investigation of quality of life in terms of utility values.
- Economic evaluations should be updated on the availability of future data.

6.2 Strengths and limitations

The strengths:

- Systematic reviews have been conducted of the clinical and cost-effectiveness of eculizumab treatment.
- Preliminary economic evaluations are provided based on existing evidence and assumptions likely to encompass all reasonable variation in important input parameters.
- Economic evaluation attempted to integrate information from multiple studies with regard to mortality and rates of thrombosis.

Limitations:

- The natural history and prognosis of PNH reviews were undertaken pragmatically.
- For economic evaluation thrombosis rate was assumed to have a linear trend.
- There is an absence of accurate estimates about costs and resource use for standard care to fully inform the economic evaluations undertaken.

7. CONCLUSIONS

The estimated prevalence of PNH in the UK (1.59/100,000) places this condition within the definition of an ultra-orphan disease.

Eculizumab is highly effective at reducing haemolysis with consequent reduced demand for transfusions and improvement in anaemia and quality of life, especially with respect to fatigue. There is evidence that eculizumab has a large impact in diminishing the probability of thrombosis in PNH patients and it is reasonable to expect this translates into improved life expectancy, but good estimates of effect sizes await further investigation. The drug is well tolerated although the short-term nature of observations of potential side effects means continued vigilance is required.

No previous economic evaluation studies for eculizumab have been identified. The limited availability of good quality scientific evidence means implementation of a fully informed model for estimation of cost-effectiveness in terms of £/QALY is impractical at this time. We have conducted three preliminary economic evaluations for the use of eculizumab. Due to lack of accurate estimates of resource use and the unit costs for standard care precise estimates of ICER in terms of £/LYG cannot be developed.

8. APPENDICES

Appendix 1 Symptoms experienced in anaemia

Part of body efffected	Compensatory mechanism	Dysfunction
Brain		Fatigue, headaches, dizziness, lack of concentration, depression
Eyes		Retinal damage
Heart	Rapid pulse, palpitations	Angina
Lungs	Rapid breathing, breathlessness	In severe cases, worsened breathlessness from pulmonary oedema and heart failure
Kidneys		Water retention
Gut	Loss of appetite	Indigestion, irregular bowel movements, impaired nutrient uptake
Muscles/legs		Fatigue, poor exercise capacity, swelling from water retention
Skin	Pallor, feeling cold	Brittle, broken nails
Reproductive organs		Increased menstrual bleeding, impotence, loss of libido
Table based closely on Wilson 2007[9]		

Appendix 2 Search strategies

Search strategy for incidence, prevalence and prognosis studies

Searches were conducted using appropriate index and text words encompassing paroxysmal nocturnal haemoglobinuria and eculizumab. Searches were not limited by date or by language. The following sources were searched for relevant studies:

- Bibliographic databases: Cochrane Library 2007 Issue 4, Embase (Ovid) 1980 – Nov 2007, MEDLINE (Ovid) 1950 – Nov 2007, and MEDLINE In-Process & Other Non-Indexed Citations Nov 21 2007.
- Citation checking of relevant studies.
- Industry internet site.
- Contact with experts and industry.

Prevalence and incidence

Source – Cochrane Library (all databases) 2007 Issue 4

#1 paroxysmal next nocturnal next haemoglobinuria 2
#2 paroxysmal next nocturnal next hemoglobinuria 13
#3 pnh 12
#4 marchiafava next michelli next syndrome 0
#5 (#1 OR #2 OR #3) 22

Source - Ovid MEDLINE(R) 1950 to November Week 2 2007

1 pnh.mp. (1027)
2 paroxysmal nocturnal haemoglobinuria.mp. (448)
3 paroxysmal nocturnal hemoglobinuria.mp. (1397)
4 marchiafava michelli syndrome.mp. (0)
5 hemoglobinuria, paroxysmal/ (2345)
6 or/1-5 (2726)
7 survey$.mp. (250649)
8 prevalence.mp. (241612)
9 incidence$.mp. (393319)
10 cohort$.mp. (144884)
11 cohort studies/ (79335)
12 or/7-11 (900799)
13 6 and 12 (110)

Source - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 21, 2007

1 pnh.mp. (33)
2 paroxysmal nocturnal haemoglobinuria.mp. (0)
3 paroxysmal nocturnal hemoglobinuria.mp. (38)
4 marchiafava michelli syndrome.mp. (0)
5 or/1-4 (50)

Source - EMBASE (Ovid)1980 to 2007 Week 46

1 pnh.mp. (807)
2 paroxysmal nocturnal haemoglobinuria.mp. (293)

3 paroxysmal nocturnal hemoglobinuria.mp. (1434)
4 marchiafava michelli syndrome.mp. (0)
5 survey$.mp. (578052)
6 prevalence.mp. (217395)
7 incidence$.mp. (320446)
8 cohort$.mp. (108449)
9 or/1-4 (1552)
10 or/5-8 (1111176)
11 9 and 12 (140)

Prognosis studies

Source – Cochrane Library (all databases) 2007 Issue 4

#1 paroxysmal next nocturnal next haemoglobinuria 2
#2 paroxysmal next nocturnal next hemoglobinuria 13
#3 pnh 12
#4 marchiafava next michelli next syndrome 0
#5 (#1 OR #2 OR #3) 22

Source - Ovid MEDLINE(R) 1950 to November Week 2 2007

1 pnh.mp. (1027)
2 paroxysmal nocturnal haemoglobinuria.mp. (448)
3 paroxysmal nocturnal hemoglobinuria.mp. (1397)
4 marchiafava michelli syndrome.mp. (0)
5 hemoglobinuria, paroxysmal/ (2345)
6 or/1-5 (2726)
7 limit 6 to "prognosis (optimized)" (170)

Source - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 21, 2007

1 pnh.mp. (33)
2 paroxysmal nocturnal haemoglobinuria.mp. (0)
3 paroxysmal nocturnal hemoglobinuria.mp. (38)
4 marchiafava michelli syndrome.mp. (0)
5 or/1-4 (50)

Source - EMBASE (Ovid) 1980 to 2007 Week 46

1 pnh.mp. (807)
2 paroxysmal nocturnal haemoglobinuria.mp. (293)
3 paroxysmal nocturnal hemoglobinuria.mp. (1434)
4 marchiafava michelli syndrome.mp. (0)
5 or/1-4 (1552)
6 limit 5 to "prognosis (optimized)" (156)

Search strategy for studies of therapy with eculizumab for PNH

The following sources were searched for relevant studies:

- Bibliographic databases: Cochrane Library 2007 Issue 4, Embase (Ovid) 1980 – Nov 2007, MEDLINE (Ovid)1950 – Nov 2007, and MEDLINE In-Process & Other Non-Indexed Citations Nov 21 2007. Searches used

index and text-words that encompassed paroxysmal nocturnal haemoglobinuria and eculizumab.

- Additional searches of HEED for economic evaluation studies.
- Citation checking of relevant studies.
- Industry internet site.
- Contact with experts and industry.
- Registers of ongoing trials: National Research Register, ClinicalTrials.gov and Controlled Clinical Trials.

Source – Cochrane Library (all databases) 2007 Issue 4
#1 paroxysmal next nocturnal next haemoglobinuria 2
#2 paroxysmal next nocturnal next hemoglobinuria 13
#3 pnh 12

#4 marchiafava next michelli next syndrome 0
#5 (#1 OR #2 OR #3) 22
#6 eculizumab or soliris 9
#6 (#5 AND #6) 8

Source - Ovid MEDLINE(R) 1950 to November Week 2 2007

1 pnh.mp. (1027)
2 paroxysmal nocturnal haemoglobinuria.mp. (448)
3 paroxysmal nocturnal hemoglobinuria.mp. (1397)
4 marchiafava michelli syndrome.mp. (0)
5 hemoglobinuria, paroxysmal/ (2345)
6 or/1-5 (2726)
7 limit 6 to "therapy (optimized)" (11)
8 (eculizumab or soliris).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (36)
9 7 or 8 (45)

Source - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 21, 2007

1 pnh.mp. (33)
2 paroxysmal nocturnal haemoglobinuria.mp. (0)
3 paroxysmal nocturnal hemoglobinuria.mp. (38)
4 marchiafava michelli syndrome.mp. (0)
5 or/1-4 (50)'.

Source - EMBASE (Ovid) 1980 to 2007 Week 46

1 pnh.mp. (807)
2 paroxysmal nocturnal haemoglobinuria.mp. (293)
3 paroxysmal nocturnal hemoglobinuria.mp. (1434)
4 marchiafava michelli syndrome.mp. (0)
5 or/1-4 (1552)
6 limit 5 to "treatment (1 term min difference)" (84)
7 (eculizumab or soliris).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (119)
8 6 or 7 (170)

Search strategy for identification of economic evaluations

Source - Cochrane Library (NHS EED) 2007 Issue 4

#1 paroxysmal next nocturnal next haemoglobinuria 2
#2 paroxysmal next nocturnal next hemoglobinuria 13
#3 pnh 12
#4 marchiafava next michelli next syndrome 0
#5 (#1 OR #2 OR #3) 22

Source- HEED (Wiley Interscience). Searched January 2008

Search terms: PNH or paroxysmal nocturnal or marchiafava or eculizumab or soliris

Search strategy for identification of ongoing trials

Source – Clinical trials.gov and Controlled Clinical Trials

A series of searches were undertaken using the following terms: paroxysmal nocturnal haemoglobinuria, paroxysmal nocturnal hemoglobinuria, pnh, soliris, eculizumab.

Appendix 3 Data extraction from graphs

Graphs were scanned into a Word document, over-layered with an appropriate template with graph gridlines, printed and enlarged to A3 size and information extracted using the gridline template. To reduce error in this procedure, extracted information was checked by comparing graph readings with any available values in the report text and/or by redrawing the graph using the extracted data and comparing this with the original.

For example data points read from figure 2 of the TRIUMPH study were fitted with exponential and Weibull distributions as shown below.

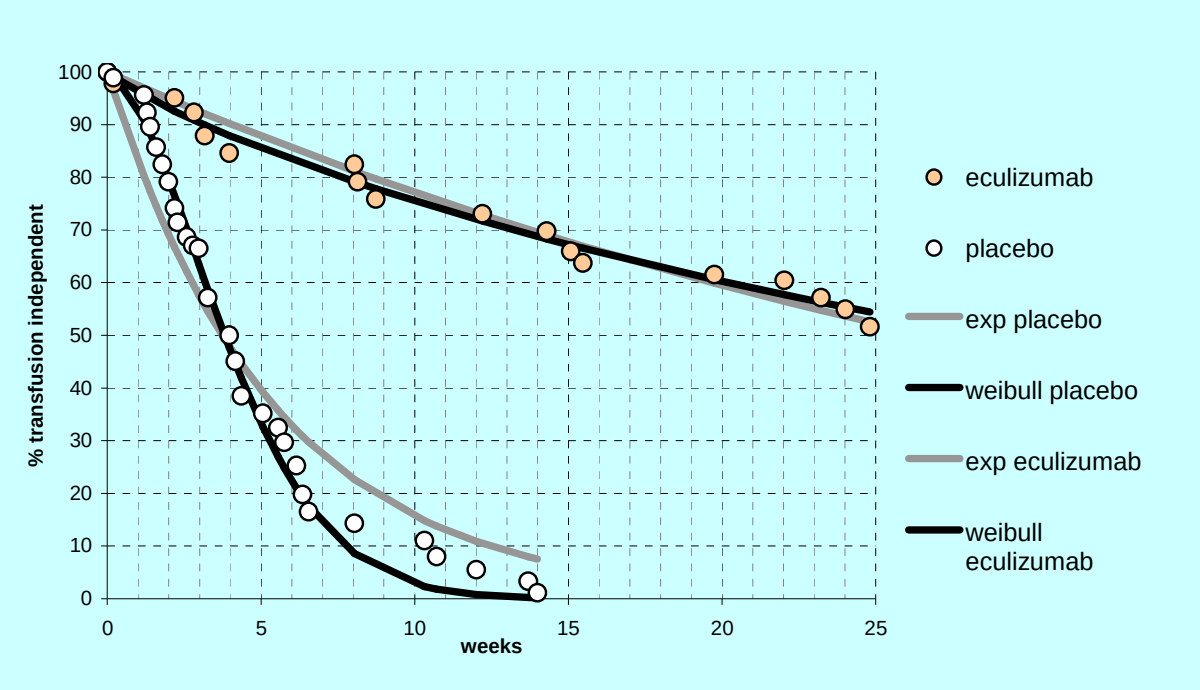

Figure 11 Proportion of patients transfusion-independent in the TRIUMPH study.

Appendix 4 Thrombosis rate for all diagnosed PNH patients without eculizumab treatment

Table 8 Thrombosis rate for all diagnosed patients without eculizumab treatment

	No. patients who had thrombosis	The total No. of patients	Thrombosis rate	
			Median	95% credible interval
Hall[20]	29	163	0.19	(0.13,0.26)
Hillmen[21]	31	80	0.36	(0.25, 0.47)
Socie[22]	59	220	0.27	(0.21,0.33)
		Pooled	0.26	(0.10,0.53)

Appendix 5 Flow diagram for retrieved studies and list of excluded studies

Table 9 Flow diagram for retrieval of effectiveness studies

Bibliographic database hits	
Medline	95
EMBASE	170
Cochrane Library	8
TOTAL	**273**
Full papers sought	18
Additional papers sought after scrutiny of reference lists of published papers	2
Total full papers	**20**
Posters obtained	2
Included full papers	5
Included posters	2 (1 as yet unpublished)
Excluded full papers	**15**

Table 10 Excluded studies and reasons for exclusion

	Study	Criterion not met / reason for exclusion
1	Bessler M. New dawn for a nocturnal disease. Blood 2005; 106(7): 2224-2225.	Study design (review)
2	Colombo GM, Guglielmelli E, Sacco T, Cicchinelli M, Colombo GM, Guglielmelli E, et al. Adverse reactions and medical approach to paroxysmal nocturnal hemoglobinuria. Minerva Medica 2007; 98(1):87-88.	Less than 10 patients
3	Eculizumab: long-acting anti-C5 monoclonal antibody 5G1-1. Drugs in R & D 2007; 8(1):61-68.	Study design (review)
4	Hill A, Hill A. Eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Clinical Advances in Hematology & Oncology 2005; 3(11):849-850.	Study design (review)
5	Hill A, Richards SJ, Hillmen P, Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. British Journal of Haematology 2007; 137(3):181-192.	Study design (review)
6	Hill A, Rother RP, Hillmen P, Hill A, Rother RP, Hillmen P. Improvement in the symptoms of smooth muscle dystonia during eculizumab therapy in paroxysmal nocturnal hemoglobinuria. Haematologica 2005; 90(12 Suppl):ECR40.	Less than 10 patients
7	Kathula SK, Kathula SK. Eculizumab in paroxysmal nocturnal hemoglobinuria. New England Journal of Medicine 2006; 355(26):2786-2788.	Study design (commentary piece)
8	Nau J-Y. Demonstration of the effectiveness of eculizumab against paroxysmal nocturnal hemoglobinuria. Revue Medicale Suisse 2006; 2 (81):2255.	Study design (review)
9	Parker C, Omine M, Richards S, Nishimura J-I, Bessler M, Ware R, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 2005; 106(12):3699-3709.	Study design (review)
10	Parker CJ, Kar S, Kirkpatrick P, Parker CJ, Kar S, Kirkpatrick P. Eculizumab. Nature Reviews 2007; Drug Discovery. 6(7):515-516.	Study design (review)
11	Pride YB, Pride YB. Eculizumab in paroxysmal nocturnal hemoglobinuria. New England Journal of Medicine 2006; 355(26):2787-2788.	Study design (commentary piece)
12	Richards SJ, Hill A, Hillmen P, Richards SJ, Hill A, Hillmen P. Recent advances in the diagnosis, monitoring, and management of patients with paroxysmal nocturnal hemoglobinuria.Cytometry Part B, Clinical Cytometry 2007; 72(5):291-298.	Study design (review)
13	Singh J, Malani AK, Pabla M, Singh J, Malani AK, Pabla M. Eculizumab in paroxysmal nocturnal hemoglobinuria. New England Journal of Medicine 2006; 355(26):2786-2788.	Study design (commentary piece)
14	Takita M, Matsumura T, Kami M, Takita M, Matsumura T, Kami M. Eculizumab in paroxysmal nocturnal hemoglobinuria. New England Journal of Medicine 2006; 355(26):2787-2788.	Study design (commentary piece)
15	Zareba KM. Eculizumab: A novel therapy for paroxysmal nocturnal hemoglobinuria. Drugs of Today 2007; 43(8): 539-546	Study design (commentary piece)

Appendix 6 Summary of results reported in the PILOT study

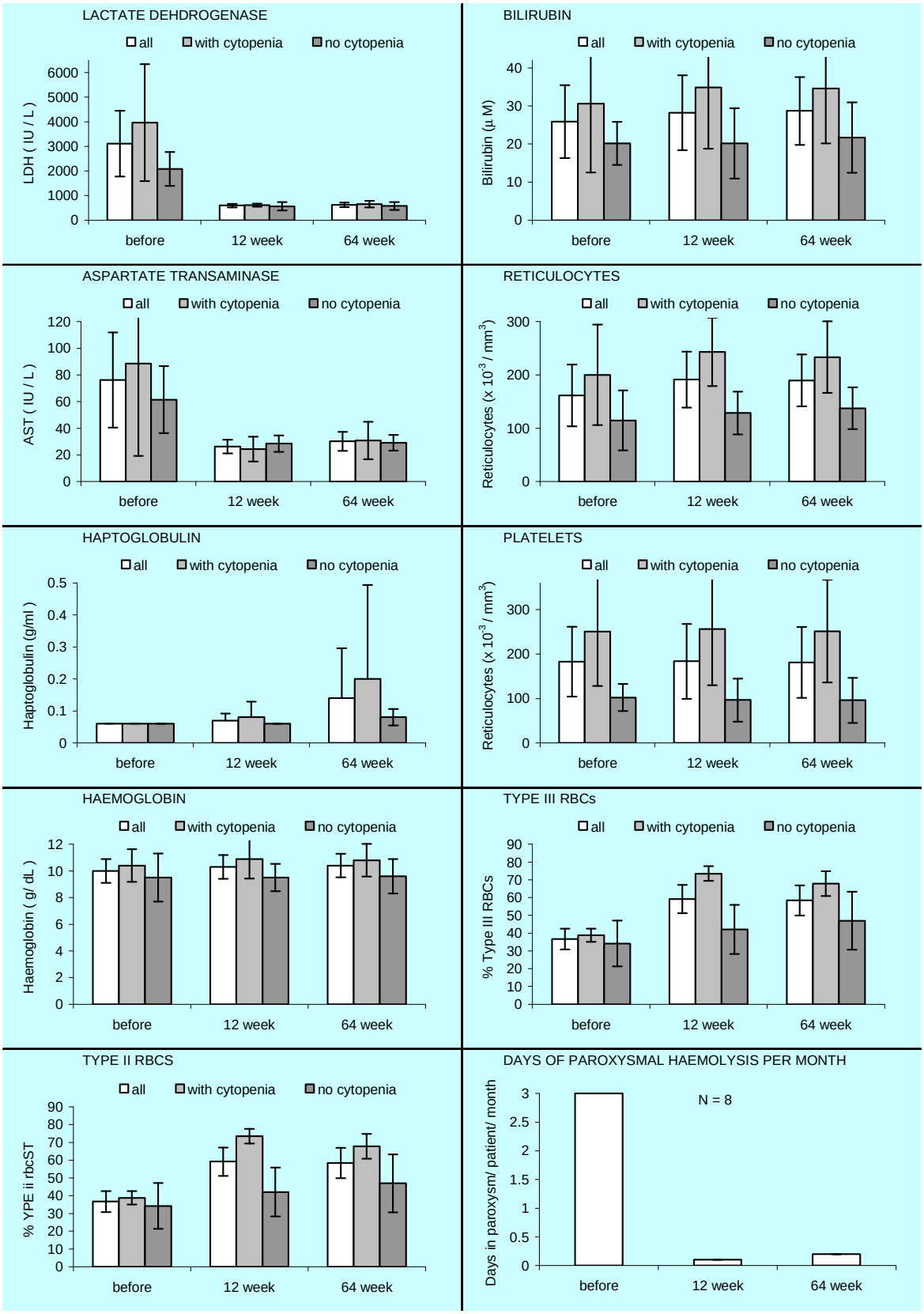

Figure 12 Levels of markers of haemolysis and platelet counts reported in PILOT study.

Error bars represent 95% confidence intervals where calculable.

Results reported in the PILOT[40,41] study are summarised in Figure 12. Compared to baseline LDH, aspartate transaminase and days/month with paroxysmal haemolysis were greatly reduced indicating reduced haemolysis with eculizumab treatment. The proportion of type II and type III RBCs increased relative to baseline, as did haptoglobulin levels while transfusion rate decreased. These changes were accompanied by a small increase in haemoglobin level. Quality of life measures estimated using the EORTC instrument were improved at week 64 relative to baseline. Overall the results are consistent with a considerable reduction in haemolysis and improvement in anaemia and quality of life with eculizumab treatment.

Appendix 7 Scoring system for the FACIT instrument

Table 11 Scoring system for the FACIT fatigue instrument.

Question	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless (washed out)	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble starting things because I am tired	0	1	2	3	4
I have trouble finishing things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

Taken from Cella et al 2002.[45]

Appendix 8 Cost effectiveness for a variety of standard care costs, savings and survival rates

The survival curves for patients treated with eculizumab or with SC (SC1, SC2, SC3) that were used in economic analysis II are shown in Figure 13 (top panel). The average LYG annually per patient for each SC survival curve is shown in the middle panel and the average cumulative LYG per patient treated is shown in the lower panel. As the cost/live patient in the treated and SC cohorts were assumed to be constant throughout the 25 year time horizon the cumulative difference in cost (treated – SC) between the cohorts has the same trajectory as the cumulative gain in life years. This means that the relationship between the ICER (eculizumab v SC) and the cost of SC is linear (see section 4.4.1). In order to explore this relationship more fully we: a) modified the Weibull distribution for SC curve SC2 so as to generate two hypothetical SC curves with median survival of 5.8 and 20 years; b) extended the cost of SC beyond £100K. In this analysis we used the assumption that treatment with eculizumab avoided 90% of the cost of SC. The results are shown in Figure 14.

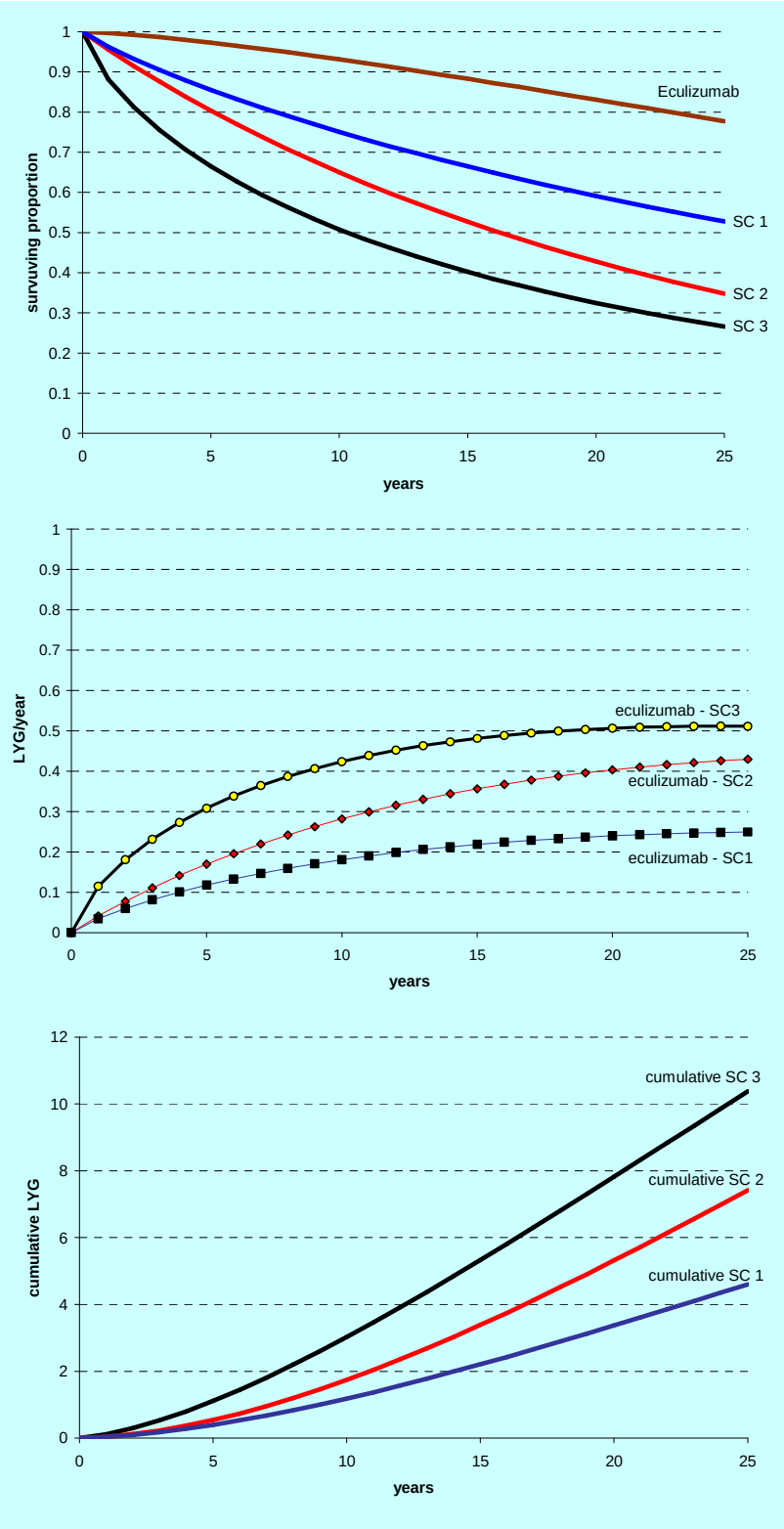

Figure 13 Survival curves and life years gained used in preliminary economic analysis II

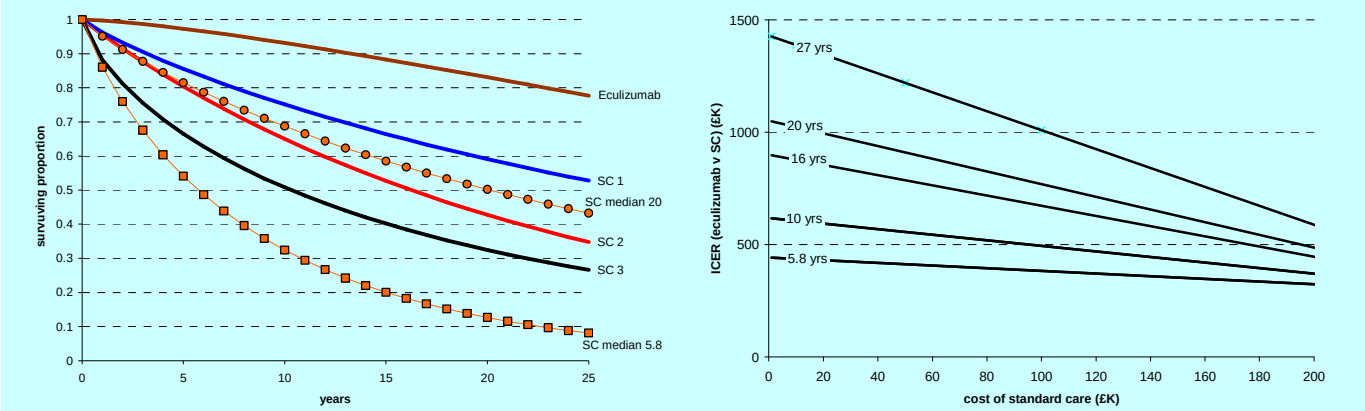

Figure 14 Survival curves and corresponding ICERs for varying standard care costs.

The median survival for standard care curves SC1, SC2 and SC3 was 27, 16, and 10.years respectively.

With low cost of SC ICERs ranged from about £0.45M/LYG to £1.4M/LYG and with SC annual cost at £200K ICERs ranged from about £0.3M to £0.6M.

Appendix 9 Mortality rate for PNH patients with thrombosis

Table 12 Mortality rate for patients with thrombosis

Study	No. patients who died of thrombosis	The total No. of patients with thrombosis	Mortality rate	
			Median	95% credible interval
Hall[20]	14	29	0.52	(0.38,0.63)
Hillmen[21]	14	31	0.51	(0.36,0.62)
Socie[22]	35	59	0.55	(0.45,0.67)
		Pooled	0.52	(0.36,0.66)
95% credible interval describes an interval of the parameter space such that the probability that the parameter's value lies in the interval is at least 95%.				

Appendix 10 Mortality rate for PNH patients without thrombosis

Table 13 Mortality rate for patients without thrombosis

Study	No. patients who was not died of thrombosis	The total No. of patients without thrombosis	Mortality rate	
			Median	95% credible interval
Hall[20]	6	134	0.05	(0.02,0.10)
Hillmen[21]	14	49	0.27	(0.16,0.41)
Socie[22]	36	161	0.22	(0.16,0.29)
		Pooled	0.15	(0.01,0.73)

95% credible interval describes an interval of the parameter space such that the probability that the parameter's value lies in the interval is at least 95%.

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