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Migalastat for Fabry disease

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors
Keith Cooper, Senior Research Fellow, SHTAC
Petra Harris, Research Fellow, SHTAC
Micah Rose, Research Fellow, SHTAC
Christian Böhler, Health Economics Independent Consultant
Maria Chorozoglou, Senior Research Fellow, SHTAC
Jonathan Shepherd, Principal Research Fellow, SHTAC
Geoff Frampton, Senior Research Fellow, SHTAC

Correspondence to
Dr Geoff Frampton
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

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Contributions of authors

Keith Cooper critically appraised the health economic systematic review, critically appraised the health economic evaluation and drafted the report; Petra Harris critically appraised the clinical effectiveness systematic review and drafted the report; Micah Rose critically appraised the health economic evaluation and drafted the report; Christian Böhler critically appraised the health economic evaluation and drafted the report; Maria Chorozoglou drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project guarantor; Geoff Frampton critically appraised the clinical effectiveness systematic review, drafted the report and project managed the report.

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LIST OF ABBREVIATIONS

α-gal A	Alpha-galactosidase A
ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
ARB	Angiotensin receptor blocker
BNF	British National Formulary
BPI	Brief Pain Inventory
CEFD	Clinically evident Fabry disease
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CS	Company's submission
CSR	Clinical study report
DCE	Discrete choice experiment
eGFR	Estimated glomerular filtration rate
$eGFR_{CKD-EPI}$	Estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration
$eGFR_{MDRD}$	Estimated glomerular filtration rate Modification of Diet in Renal Disease
ESRD	End stage renal disease
ERG	Evidence review group
ERT	Enzyme replacement therapy
FDA	Food and Drug Administration
GLA	Gene for aplpa galactosidase A
GL3	Globotriaosylceramide
HRG	Healthcare Resources Group
HRQL	Health-related quality of life
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat (population)
LSD	Lysosomal storage disorder
LV	Left ventricular

LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
mGFR	Measured glomerular filtration rate
$mGFR_{iohexol}$	Glomerular filtration rate measured - iohexol
MI	Myocardial infarction
mITT	Modified intention to treat (population)
NYHA	New York Heart Association
OLE	Open-label extension
ONS	Office for National Statistics
PBMC	Peripheral blood mononuclear cells
PPS	Personal social services
PRO	Patient-Reported Outcome
PSSRU	Personal Social Services Research Unit
RRR	Relative risk reduction
QALY	Quality-adjusted life year
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36 Health survey
TIA	Transient ischaemic attack
UA	Unstable angina
ULN	Upper limit of normal
VT	Ventricular tachycardia
WBC	White blood cell

SUMMARY

Scope of the company submission

The company's submission (CS) is mostly reflective of the scope of the evaluation issued by NICE. The population is people aged 16 years or over with a confirmed diagnosis of Fabry disease, who have an amenable mutation in the *GLA* gene (the scope does not specify age, although the population being aged 16 and above is consistent with the expected licensed indication). The intervention is migalastat, administered orally as a capsule containing 150 mg of migalastat hydrochloride (equivalent to 123 mg migalastat) once at the same time every other day. This is in line with the expected marketing authorisation. The comparator is enzyme replacement therapy (ERT), with either agalsidase alfa or agalsidase beta, although the CS employs a 'blended' comparator which does not distinguish between agalsidase alfa and beta. The company has presented evidence from two randomised controlled trials (RCTs). One of these involved ERT as the comparator and is directly relevant to the scope ('ATTRACT') whilst the other RCT employed a placebo as the comparator, which is not directly relevant to the scope ('FACETS'). The company also presented clinical evidence from single-arm open-label extension (OLE) studies that followed the two RCTs. All the outcomes specified in the scope are included in the company's decision problem. However, only limited information from the relevant RCT is used to inform the company's economic analysis.

Summary of submitted clinical effectiveness evidence

The CS presents evidence of the clinical effectiveness of migalastat based on two RCTs and two subsequent OLE studies, all of which were sponsored by the company. In all these studies migalastat was taken as an oral capsule of 150mg migalastat hydrochloride once every other day.

The 'ATTRACT' RCT was open-label and compared migalastat against ERT over an 18-month period in patients who had previously received ERT. Patients were randomised to either continue receiving ERT or to switch from ERT to migalastat. Primary outcomes were changes in renal function assessed by measured and estimated glomerular filtration rates (mGFR and eGFR). According to the literature and clinical advice received by the ERG, measured mGFR is more reliable than eGFR.

The ‘FACETS’ RCT was double-blind and compared migalastat to placebo over a 6-month period in patients who had not previously received ERT within 6 months of eligibility screening. The primary outcome was a biochemical measure: changes in inclusions of globotriaosylceramide (GL3) in interstitial capillary cells. Being a placebo-controlled trial, FACETS is not directly relevant to the scope, and results from this trial did not inform the company’s economic analysis. However, as the evidence base for migalastat is small, the ERG has summarised and critiqued the findings from all the clinical effectiveness studies included by the company.

IN ATTRACT, the ERT group comprised patients who were receiving agalsidase alfa or agalsidase beta, but the proportions receiving each of these drugs was not specified. A standard non-inferiority analysis comparing migalastat and ERT on the co-primary endpoints was not possible due to the small sample size. The use of descriptive statistics was agreed during scientific advice with the EMA/CHMP. The company in conjunction with the EMA agreed that migalastat has ‘comparable’ effectiveness to ERT if two criteria were met: differences between migalastat and ERT groups in annualised changes in mGFR and eGFR were within a pre-specified limit of 2.2 mL/min/1.73m2; and confidence intervals for the mean change in these renal outcomes in the migalastat and ERT groups had greater than 50% overlap

The CS states that these criteria were agreed with the European Medicines Agency (EMA) and the ATTRACT interim clinical study report (CSR) mentions that they were pre-specified. However, the company provides no justification for these criteria and the ERG has been unable to verify the process whereby these were developed and agreed.

As secondary outcomes, both RCTs reported renal function, cardiac function, health-related quality of life (HRQoL), biochemical outcomes, and adverse events. Additional data on longer-term outcomes following the ATTRACT and FACETS RCTs are presented in the CS as ongoing, single-arm, OLE studies, in which patients from all the trial arms in ATTRACT and FACETS could continue to receive 150 mg migalastat hydrochloride once every other day for up to a further 18 months.

Adverse events data are presented for the two identified RCTs and for the OLE studies. Although the company’s searches included non-randomised studies, specific eligibility criteria for identifying relevant studies of migalastat safety are not provided.

No meta-analyses were conducted. The company provided a rationale for why an indirect comparison using network meta-analysis was not feasible and the ERG concurs with this.

Quality of the evidence

Overall, the searches conducted by the company are considered by the ERG to be appropriate and likely to have identified all relevant evidence. An anomaly is that HRQoL outcomes were identified from the review of clinical effectiveness and also from a review of HRQoL studies, but only the latter review provided HRQoL data for the company's economic analysis. Non-randomised studies were not explicitly searched for adverse events, but the company presents a brief overview of adverse events encountered during its migalastat research and development programme, which was based on both randomised and non-randomised studies.

The ERG has some concerns about the quality of the ATTRACT and FACETS RCTs. Despite randomised group allocation, there were baseline imbalances in patient characteristics between the trial arms in both RCTs. In the ATTRACT trial these relate to mean age (4 years older in the migalastat group), mean time since diagnosis (3.2 years shorter in the migalastat arm), and mean 24-hour urine protein (93 mg less in the migalastat arm). Although intention to treat (ITT) analysis was undertaken based on all randomised patients in both trials, the ITT populations included patients who were found after randomisation not to have amenable mutations (6% and 8% of patients in the migalstat and ERT arms of ATTRACT, and 18% and 33% of patients in the migalastat and placebo arms of FACETS). The CS therefore emphasises the results of 'modified ITT' (mITT) analyses, which exclude these patients. In the ATTRACT RCT, the mITT population excluded patients with other protocol violations, as well as non-amenable mutations, and was effectively a per protocol population. The term 'modified ITT' is therefore potentially misleading (and has a different meaning in the two RCTs).

Evidence of the effectiveness of migalastat - ATTRACT trial

In the ATTRACT RCT, the mean annualised change over 18 months in mGFR (mL/min/1.73m^2) according to ITT analysis was [redacted] in the migalastat group (n=36) and [redacted] in the ERT group (n=24) (between-groups difference [redacted] The respective changes in the mITT analysis were −4.35 (95% CI −7.65, −1.06) in the migalastat group (n=34) and −3.24 (95% CI −7.81, 1.33) in the ERT group (n=18) (between-groups difference −1.11). The CS also reports data for 30 patients who received migalastat in

ATTRACT and who continued on migalastat in the OLE period and provided sufficient data to calculate the 30-month mean annualised rate of change in GFR. The mGFR showed a decline, −2.7 (95% CI −4.8, −0.7) mL/min/1.73m^2, with the 95% confidence interval not overlapping zero. Changes in 24-hour urine protein and in the albumin:creatinine ratio were reported in addition to the GFR outcomes, but only for the mITT analysis. The 0-18 month change in mean urine protein was [redacted] mg/day in the migalastat group (n=34) and [redacted] mg/day in the ERT group (n=18) (between-groups difference [redacted] mg/day). The respective changes in the mean albumin:creatinine ratio were [redacted] mg/nmol in the migalastat group and [redacted] mg/nmol in the ERT group (between-groups difference [redacted] mg/nmol). Whilst the point estimates indicate a slower rate of decline of renal function in the migalastat group than the ERT group, the confidence intervals included zero, indicating lack of a significant difference.

The ATTRACT trial reported cardiac outcomes only for mITT analyses. The 0-18 month change in median left ventricular ejection fraction (LVEF) was [redacted]% in the migalastat group and [redacted]% in the ERT group (between-groups difference [redacted]%) (the CS does not specify whether the variance measure reported for the medians is the confidence interval or inter-quartile range). The respective changes in the mean left ventricular mass index (LVMI) were −6.6 (95% CI −11, −2.2) g/m^2 in the migalastat group (n=34) and −2 (95% CI −11, 7) g/m^2 in the ERT group (n=18) (between-groups difference −4.6 g/m^2). These results suggest migalastat did not detectably influence LVEF, but did improve left ventricular mass.

Changes in biochemical outcomes reported in ATTRACT did not differ significantly from zero, except that activity of the target enzyme α-galactosidase A in white blood cells increased significantly in the migalastat group but not the ERT group. This change reflects the mode of action of migalastat, but the outcome is not used consistently in clinical decision making.

HRQoL was assessed using the Short Form 36 (SF-36) and the Brief Pain Inventory (BPI). The analysis population for HRQoL was smaller than the mITT population, as only mITT population patients who had complete HRQoL records were analysed (for the ERT group, which had the fewest patients, the sample size was only n=16 for the SF-36 and n=17 for the BPI). Mean scores for the SF-36 Physical Component Summary, SF-36 Mental Component Summary and the BPI increased marginally in the migalastat group over 18 months and slightly decreased in

the ERT group; however, the differences were small and the confidence intervals in all cases included zero.

Evidence of the effectiveness of migalastat - FACETS trial

The primary, biochemical, outcome in the FACETS trial was the six-month change from baseline in the proportion of patients who had a ≥50% reduction in interstitial capillary GL3 inclusions, analysed in the ITT population. This was higher in the migalastat arm (40.6%; n=34) than the placebo arm (28.1%; n=33), but the difference between groups was not statistically significant.

For renal function (secondary outcome), the six-month change in mean (±SE) mGFR in the ITT analysis in FACETS was −1.19 ± 3.4 mL/min/1.73m^2 in the migalastat group (n=34) and 0.41 ± 2.0 mL/min/1.73m^2 in the placebo group (n=33). Although these results suggest that patients may have had better stabilisation of GFR in the placebo group than the migalastat group, six months is likely too short to draw any firm conclusions about changes in renal function, especially given the relatively small sample sizes and large standard errors. The CS also reports the mean change in mGFR for FACETS patients who continued on migalastat for a further 18 months in the OLE period, but it does not distinguish between those who received a total of 18 months of migalastat (6 months of placebo in FACETS + 18 months of migalastat in the OLE) and those who received a total of 24 months of migalastat (6 months of migalastat in FACETS + 18 months of migalastat in the OLE). The mean change in GFR from 0-24 months for these two groups combined was −1.51 (95% CI −4.20, 1.18) mL/min/1.73m^2 (n=37). The FACETS trial also reported two different measures of eGFR, but these showed inconsistent changes from baseline.

FACETS did not report quantitative results for both the trial arms for any other renal outcomes, for any cardiac outcomes, or for HRQoL assessed using the SF-36 or BPI. Quantitative HRQoL results were reported for the Gastrointestinal Symptoms Rating Scale (GSRS. Changes in GSRS scores suggested a greater improvement in diarrhoea and reflux symptoms in the migalastat group compared to the placebo group, but no difference between the groups for indigestion, constipation or abdominal pain. However, sample sizes were not reported. Due to the short duration of the trial it is inadvisable to attempt to draw any firm conclusions about effects of migalastat on HRQoL.

Adverse events

The most frequent adverse events in the ATTRACT RCT were nasopharyngitis and headache, and these did not differ in frequency between the migalastat and ERT groups. No deaths occurred in either RCT or in the OLE studies. The CS states that no patients discontinued due to treatment-emergent adverse events in either RCT. Overall, the adverse events data submitted by the company do not raise any safety concerns over the use of migalastat. However, a potential limitation of the adverse events data is that the RCTs were of relatively short duration and the numbers of patients who completed the OLE studies were small ([redacted] patients from ATTRACT received a total of 30 months of migalastat therapy, whilst [redacted] patients from FACETS received a total of 24 months of migalastat therapy).

Summary of submitted cost effectiveness evidence

The company's cost consequence analysis uses a Markov model to estimate the costs and health effects of migalastat compared with ERT in people with Fabry disease. The starting population is Fabry disease patients with an amenable mutation who are at least 16 years old and have no end stage renal disease (ESRD) at baseline. The proportion of female patients is 50% based on clinical expert opinion. The ERTs included in the model are agalsidase alfa and agalsidase beta, in line with the NICE scope and the ATTRACT trial. However, there is no evidence available from head-to-head comparisons of these therapies. Therefore, the CS assumes that they are clinically equivalent and the comparator used in the model is a 'blended' ERT comparator. The costs for treatment and administration are based on the market share of the two ERTs, 70% and 30% for agalsidase alfa and agalsidase beta respectively. The market share is based on clinical expert opinion.

Cardiac complications, ESRD and stroke are considered the most important symptoms of Fabry disease and therefore form the basis of the model health states. The structure of the Markov model is based on a Dutch cost effectiveness analysis study,[1] chosen to reflect the clinical pathway and progression of the disease symptoms. Patients' progression through the model is based upon the course of the disease, with the number of organ systems affected increasing over time. Disease progression in the model is captured through transitions from the neuropathic pain and clinically evident Fabry disease (CEFD) health states to the incidence of a single major complication (cardiac, stroke, or ESRD), then a combination of two major complications, and then all three. Mortality can occur in any health state. Within each health

state there is a range of possible events which contribute to the cost associated with the health state.

The analysis is from an NHS and personal social services (PSS) perspective for the base case and a societal perspective was explored in sensitivity analysis. The cycle length is one year and the analysis has a lifetime horizon. Mid-cycle correction is applied to costs and health benefits.

The transition probabilities between health states are based on the Dutch model and were estimated using data obtained from the Dutch Fabry cohort. This cohort consisted of all registered patients in the Netherlands with a diagnosis of Fabry disease. Data for 142 patients, including all paediatric patients, was collected prospectively since the availability of ERT from 1999 to the end of 2010. The effect of ERT was estimated compared to a no-treatment group by adjusting for the relative risk reduction due to treatment. In the base-case CS model, the treatment effect of migalastat was considered to be equal to the treatment effect of ERT (i.e.no difference in the transition probabilities between the two treatments).

HRQoL is included in the model through the use of utility values assigned to each health state. These values were obtained from Rombach and colleagues,[1] which were estimated using the EQ-5D questionnaire completed by 57 patients treated with ERT in the Dutch Fabry cohort. Disutilities due to acute events (cardiac, stroke and ESRD), as well as due to other ongoing adverse events (headache, influenza, dyspnoea, infections, and gastritis) are accounted for in each health state and are further explored in scenario analyses using alternative data sources from the literature review. Given that migalastat and ERT are assumed to be equivalent in terms of incidence of the three major complications and mortality, the difference in QALYs estimated in the CS derives from utility decrements due to infusions for ERT treatment and adverse events.

Costs are included for interventions (drug costs), administration costs for ERT, health state costs, follow up costs, and adverse events costs. Migalastat is an oral treatment taken once every two days and will be available in a pack with 14 capsules at a list price of £16,153.85 per pack (£210,000 per year).
The company's economic evaluation makes a number of assumptions: both ERT and migalastat, are clinically equivalent; there is no discontinuation of treatment for migalastat; clinical practice and contact with health care in the UK is similar to that in the Dutch cohort;

adherence to treatment is assumed to be 100%; the ERT is assumed to be 50% nurse-administered and 50% self-administered; and there is a discount on the cost of ERT to the NHS, assumed to be 3%.

The company's base case estimated that migalastat was associated with a discounted incremental lifetime cost of £1,268,674 compared to ERT, with an increase of 0.98 quality-adjusted life year (QALY). Sensitivity analyses were conducted on parameter estimates and additional scenario analyses to investigate specific model assumptions and inputs. The most influential parameters were discount rates, transition probabilities for treated patients, discontinuation rates, the disutility of infusions, and the market shares of the two ERTs.

The company submitted a budget impact analysis that estimated the projected costs of migalastat and ERT treatment over the next five years, based upon estimates of the number of patients eligible for treatment. The company estimated that there are currently 142 patients in England eligible for migalastat and this will increase in line with population growth such that there will be 148 eligible patients in year 5. They estimated that the cost of treating patients with Fabry disease could increase from £20,200,717 without migalastat in year 5 to [redacted] if migalastat is recommended and adopted for most patients, i.e. an increase of [redacted]

Commentary on the robustness of the submitted evidence

Strengths

The company's approach for identifying relevant evidence is generally appropriate and clearly described, and all relevant studies have been included. Extensive results from the pivotal ATTRACT and FACETS RCTs are provided together with the results of related OLE studies.

The structure of the economic model appears to represent a reasonable summary of disease progression. Utility data were derived from patients with Fabry disease, with the notable exception of disutility for infusions.

Weaknesses and areas of uncertainty

Although the ATTRACT trial is directly relevant to the scope and extensive results are presented from ATTRACT and the related OLE studies, the only outcomes from ATTRACT that directly informed the company's economic analysis were adverse events. HRQoL data for the economic

analysis were sourced from a Dutch cohort study. Renal outcomes from ATTRACT are not used directly in the economic analysis, but are cited as supporting the company's key assumption that migalastat and ERT are clinically equivalent. However, there is uncertainty around the clinical effectiveness of migalastat compared to ERT, since the ATTRACT trial was not large enough to demonstrate superiority or non-inferiority to ERT.

The placebo-controlled FACETS trial is reported in detail but is not directly relevant to the scope. It is limited by its short 6-month duration and it does not inform any of the company's economic analyses.

The majority of transition probabilities between health states in the company's economic model do not vary by patient age, leading to considerable overestimation of life expectancy in patients with Fabry disease.

There is uncertainty around the estimates chosen for the disutility associated with having an ERT infusion and the utility values for the health states used in the company model. The disutility for an ERT infusion in the model is larger than experienced by patients who move from the clinically evident Fabry disease state to ESRD, cardiac complications or stroke. This is clearly unrealistic.

Summary of additional work undertaken by the ERG

The ERG undertook analyses that: more closely reflect the health of patients with Fabry disease; corrected erroneous background mortality data used in the model; calibrated the model to replicate expected survival in Fabry disease patients; assumed an equivalent discontinuation rate from migalastat as is modelled for ERT; and assigned more plausible utility values for health states and utility decrements for infusions. Additionally, we tested assumptions about the continuation of treatment for migalastat patients who develop ESRD. Threshold analyses clearly demonstrate that transition probabilities which the model takes from the Dutch study are unrealistic.

The results of these analyses decreased costs, life-years and QALYs, but had a greater effect on incremental QALYs for migalastat than on incremental costs or life-years. The results of the ERG base case (with blended ERT) indicate that migalastat results in £890,539 of additional costs and 0.34 additional QALYs over the lifetime of a patient beginning treatment at age 40

years. These results represent a decrease in incremental costs from the list price company base case of £298,309 and a decrease in incremental QALYs of 0.54.

1 INTRODUCTION TO THE ERG REPORT

This report is a critique of the company's submission (CS) to NICE from Amicus on the clinical effectiveness and cost effectiveness of migalastat for Fabry disease. We identify the strengths and weaknesses of the CS. A clinical expert was consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 8th April 2016. A response from the company via NICE was received by the ERG on 27th April 2016 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of the company's description of the underlying health problem

The company submission (CS) provides an extensive overview of Fabry disease (also known as Anderson-Fabry disease) (CS sections 6.1 to 6.3). The overview clearly describes the underlying cause of the disease, its different phenotypes, age of onset, and the course of the disease and its morbidities.

Fabry disease is a rare inherited disease which belongs to a group of conditions known as lysosomal storage disorders (LSD). In LSD, deficiencies of certain enzymes occur which inhibit the ability of the lysosomes present in each of the body's cells to perform their normal function. This leads to an abnormal build-up of toxic materials in the body's cells causing symptoms and, eventually, organ damage and premature death. Fabry disease is closely related to a group of LSD known as mucopolysaccharidoses. In mucopolysaccharidoses the deficient enzymes affect carbohydrate metabolism, whereas in Fabry disease the deficient enzyme affects metabolism of glycolipids and glycoproteins. Although Fabry disease is not strictly a mucopolysaccharidosis, the National Mucopolysaccharidosis Society in England (MPS Society) provides advice and support for Fabry disease patients and their carers.

Fabry disease is caused by mutations in the *GLA* gene, which encodes the enzyme alpha-galactosidase A (α-gal A). Over 800 pathogenic mutations of *GLA* have been identified, with the majority causing misfolding of the enzyme which renders it non-functional or only partially

functional, preventing its normal trafficking from the endoplasmic reticulum into lysosomes. Decreased activity of α-gal A in lysosomes results in the accumulation of enzyme substrates, which cause cellular damage in tissues throughout the body. These toxic substrates include globotriaosylceramide (Gb3, also referred to as GL3) and globotriaosylsphingosine (lyso-Gb3). Chronic accumulation of these substrates over many years leads to irreversible organ damage, particularly in the nervous system, endothelium, kidney and heart, resulting in progressive kidney and heart disease, and increased risk of stroke at a relatively young age. Different *GLA* mutations vary according to whether they cause a complete or partial reduction in α-gal A activity, and the variation in α-gal A activity contributes to variation in the severity of the disease.

Fabry disease is inherited as an X-linked disorder, as the *GLA* gene is located on the X-chromosome. All males who inherit a pathogenic *GLA* mutation will develop Fabry disease and in general the disease is more severe in males than in females. Fabry disease can be divided into two main phenotypes, 'classical' and 'variant' (or 'non-classical'), and these are summarised briefly in the CS (Table B6.1). The ERG has combined the information in CS Table B6.1 with information from the literature[2] to provide an overview of these Fabry disease phenotypes (Table 1). The classical phenotype is characterised by low or no residual α-gal A activity resulting in a 'classic' set of signs and symptoms that predominantly affects males, whereas the variant phenotype reflects more variable α-gal A activity leading to more variable presentation. The variant phenotype predominantly affects heterozygous females, but also some males.

The heterogeneity of presentation in females can be explained in part by lyonization (random X chromosome inactivation) which means that *GLA* gene functionality and hence α-gal A activity can be very variable, such that some females with *GLA* mutations may be asymptomatic whilst others may have severe symptoms as in the classic phenotype disease. As shown in Table 1, specific cardiac and renal variants can be identified within the non-classical Fabry phenotype, in which the disease affects mainly the heart and kidneys respectively. The clinical advisor to the ERG commented that, until recently, the scientific literature mainly described classical Fabry disease; however, with the increased use of genetic testing, more cases of variant disease are being identified and the variant phenotype is now recognised to be more prevalent than previously thought.

Table 1 Features of the classical and variant phenotypes of Fabry disease

Classical Fabry disease	Variant (non-classical) Fabry disease
• Affects predominantly males, but also some females • Low or no residual α-gal A activity • Usually early onset • Relatively homogeneous phenotype with full spectrum of symptoms and shortened life expectancy Symptoms in childhood/adolescence: • Acroparesthesia (severe neuropathic pain in hands and feet induced by exercise, heat or fever) • Possible abdominal pain, diarrhoea or unexplained periods of fever • Clustered angiokeratoma (typical hallmark of classical disease) Symptoms in 2nd decade: • Proteinuria and/or hyperfiltration (later followed by gradual deterioration) • Kidney disease may become apparent Symptoms in 4th and 5th decades: • Possible end-stage renal failure (renal transplantation is effective but does not prevent further disease manifestations) • Bradycardia or other rhythm disturbances, followed by diastolic dysfunction and concentric hypertrophy Late stage symptoms: • Possible fibrosis, which is associated with increased prevalence of rhythm disturbances • Many patients need a pacemaker or implantable cardioverter-defibrillator • Increased risk of strokes and transient ischaemic attacks • Hearing loss and sudden deafness	• Affects heterozygote females and some males with residual α-gal A activity • α-gal A activity, and hence disease manifestation variable • Usually later onset • Variable phenotype, may be limited to one organ system, at least initially Females • Can be symptomless • Clinical symptoms include abdominal pain, fatigue, palpitations, increased sweating, joint pain, libido loss; often have neurological and cardiac symptoms, and proteinuria • Lower prevalence and later onset of kidney impairment than classically affected males Males • Clinical symptoms include acroparesthesia at young age; but cornea verticillata and clustered angiokeratoma are absent Specific variants of Fabry disease: Cardiac variant (the most common) • Primarily affects the heart, although renal disease may become apparent at a much later stage; manifests with nonobstructive cardiomyopathy and myocardial infarction Renal variant • Residual α-gal A activity and absence of typical features; presents in midlife and progresses to ESRD

Source: combined information from Hollack & Weinreb (2015) [2] and from CS Table B6.1

Fabry disease has many symptoms, which vary in age of onset, severity, and manner of progression.[3-5] Symptoms can include short term severe pain or burning sensations starting at

the extremities and spreading throughout the body (often referred to as a 'Fabry crisis'), gastrointestinal complications (e.g. diarrhoea, nausea and/or abdominal pain), headaches, inability to sweat properly (anhydrosis or hypohidrosis), vertigo, and hearing impairment (e.g. tinnitus, hearing loss). Patients may need to reduce events that trigger painful crises, such as physical exertion and emotional stress.[3] Lysosomal accumulation of Gb3 starts from the prenatal period,[6] with symptoms usually developing in early childhood after a latent period of variable duration. While symptoms usually worsen as patients get older, pain often improves after childhood.[7]

Early diagnosis is vital, as late recognition and diagnosis may mean that end organ damage is irreversible.[8] However, misdiagnosis of Fabry disease is common due to the many associated disease symptoms.[9] The MPS Society suggest in their consultee submission for the current appraisal that in England the diagnosis of Fabry disease is rarely made in children under 12 years of age unless there is an existing family history, i.e. a parent, grandparent, sibling or extended family member receives a diagnosis of Fabry disease. Enzymatic analysis of leucocyte or plasma α-gal A and/or DNA analysis of the *GLA* gene may confirm the presence of the disease in men, but in women genotyping is essential, as α-gal A concentrations of the female heterozygote may lie within the normal range.[3]

Classical Fabry disease typically has a much earlier onset and is more severe than variant Fabry disease, which results in shorter life expectancy in male than in female Fabry disease patients. Based on a large international Fabry disease registry (2848 patients), the life expectancy of people with Fabry disease has been estimated as 58.2 years in males and 75.4 years in females.[10] In comparison with the general UK population,[11] this would represent a reduction of life expectancy of approximately 21 years in males and 8 years in females. Other reports have mentioned that the lifespan may be shortened by approximately 20 years in males and 15 years in females with Fabry disease,[3, 8] although one of these reports did not cite a source[3] and the other provided data (males only) from a cross-sectional study of the UK Fabry cohort, with a relatively small sample size (98 hemizygous males).[8]

2.2 Critique of the company's overview of current service provision

The CS provides an in-depth overview of current NHS service provision for Fabry disease patients (CS section 8). The CS lists the Highly Specialist Lysosomal Storage Disorder (LSD)

Centres in England which provide diagnosis, assessment and treatment for patients (CS page 51),but the clinical advisor to the ERG commented that the Highly Specialist Centres providing Fabry disease services in England are different to the LSD centres listed in the CS: the centres providing services for adults are Addenbrookes Hospital, University College London Hospital, Royal Free Hospital London, Salford Hope Hospital, and University Hospital Birmingham; whilst those providing services for children are Birmingham Children's Hospital, Central Manchester Children's Hospital, and Great Ormond Street Hospital.

Enzyme replacement therapy (ERT) is the current cornerstone of Fabry disease management and replaces the missing or deficient α-gal A enzyme. There are two available ERT for Fabry disease: agalsidase alfa and agalsidase beta and both appear to be well tolerated.[3] Based on information supplied by clinical experts, the CS suggests that the estimated market share for ERT is 70% for agalsidase alfa and 30% for agalsidase beta. Information received in the consultee submission from the MPS Society (survey) suggests a market share of around 60% for agalsidase alfa and 40% for agalsidase beta. The ERG's clinical advisor agreed that the 60/40 split is more likely to be accurate.

UK guidelines do not recommend a particular ERT.[9] A comprehensive review of the literature published in 2010 found that no definitive conclusion can be drawn from studies that have directly compared therapeutic responses between the two commercially available enzyme preparations.[12]

Treatment is life-long, as the enzyme remains deficient throughout life. ERT cannot reverse the disease process or prevent adverse outcomes such as kidney failure[13] and is less effective in patients who have already developed fibrosis.[14] Antibody reactions to ERT often occur in males and, although these are usually easily controlled with infusion rate reductions and administration of pre-treatment medications, neutralising antibodies can reduce the effectiveness of ERT. However, patients not experiencing any symptoms may not be motivated to remain on ERT.[13] Regardless of the patient's response to ERT, symptom treatments will also be required such as for chronic pain (anticonvulsant or non-steroidal anti-inflammatory drugs) as well as more significant interventions, e.g. implantable cardio-defibrillators for tachyarrhythmia, pacemakers for bradyarrhythmia, and dialysis and renal transplant.

To ensure prompt diagnosis, the NHS standard contract for the LSD Service has a care pathway for children.[15] The CS provides a copy of the flow diagram for the paediatric care pathway (CS Figure B8.2) and states that whilst a similar diagram is not described in the NHS standard contract for metabolic disorders for adults, it is understood that a similar pathway applies to adults with Fabry disease. The paediatric care pathway is reproduced below in Figure 1. It is important to note that whilst the care pathway covers Fabry disease it also covers other LSDs and so some elements in the flow chart would not be relevant to Fabry disease care.

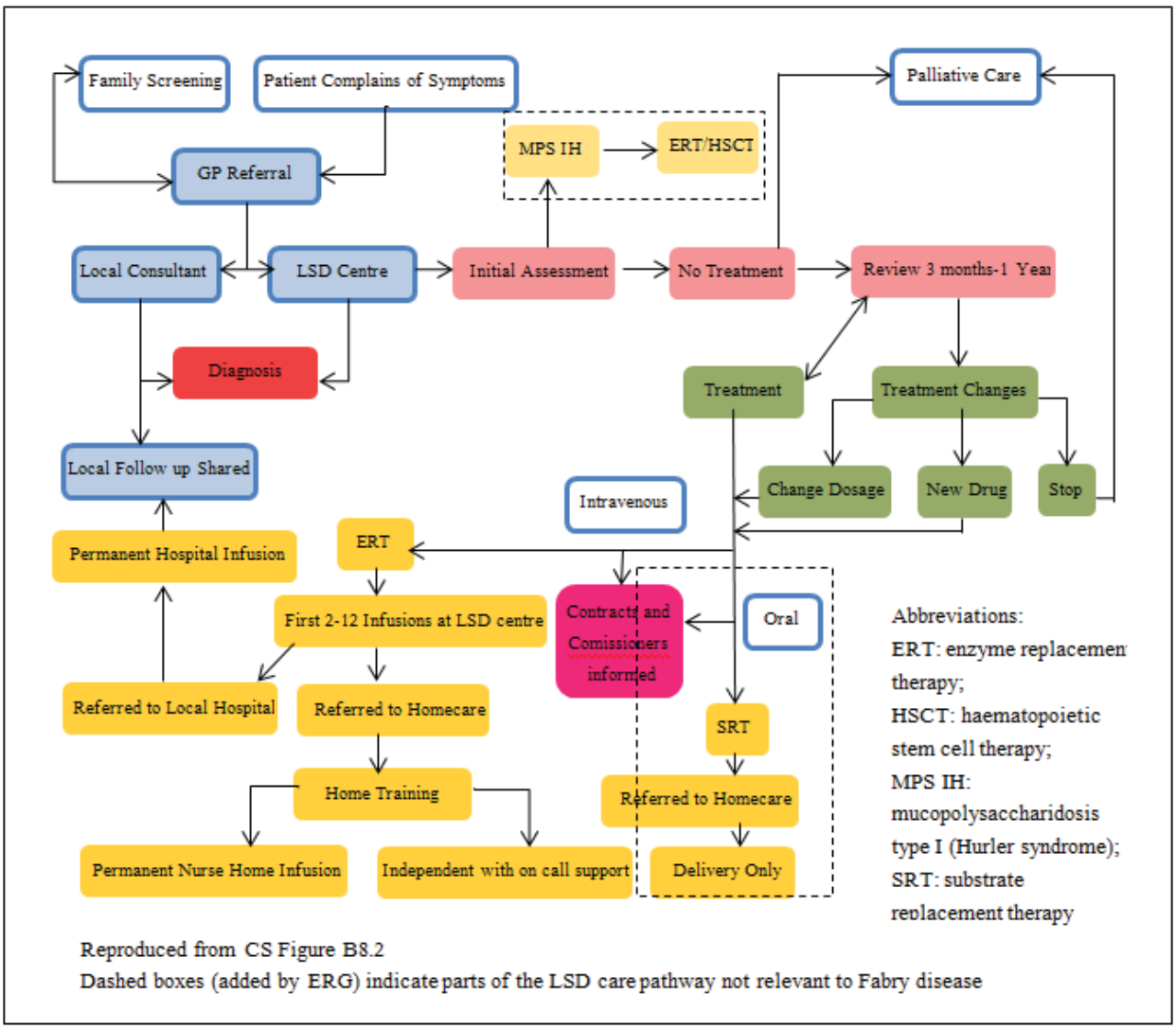

Figure 1 NHS England care pathway for the paediatric LSD Service

According to the NHS care pathway for the paediatric LSD service[15] (Figure 1), patients are identified by the GP either through family screening or due to complaints of symptoms and

would be referred to a local consultant or an LSD centre for an initial assessment. Children requiring ERT would receive their first 2-12 ERT infusions at a LSD centre and then may either receive infusions in local hospitals (if needing 'permanent hospital infusions') or at home, with home training for independent infusions or on-call support for 'permanent nurse home infusions'. Children not on ERT treatment would be reviewed after between three and 12 months, or referred to palliative care. Those on ERT treatment would be reviewed on the same basis in order to assess the need to change the dosage or the drug, or to stop treatment and refer to palliative care. The CS suggests that according to clinical experts in England, adult patients with Fabry disease would be reviewed on an annual basis if not receiving ERT, or 6-monthly when on ERT.

The CS mentions that the majority of new index cases with Fabry disease are referred by cardiologists and nephrologists, and many patients are diagnosed through family screening. Expert clinical advice received by the ERG is that in the current treatment pathway, adult patients are referred to the specialist centre either from GPs or secondary care (usually referred by cardiologists, nephrologists or neurologists) as in the paediatric flowchart. The specialist centre provides an assessment as to whether the patient meets the treatment criteria and as to whether intervention is needed for cardiac or renal involvement, in which case suitable referrals are made. For those eligible for ERT, only three infusions are given in hospital before switching the patient to home care. Patients on ERT are reviewed 6 monthly and those not meeting the criteria for ERT are generally reviewed on an annual basis. Patients are referred to palliative care if required, but this is not part of the pathway.

2.3 Critique of the company's definition of the decision problem

Population

The population described in the statement of the decision problem (people with Fabry disease with a confirmed *GLA* mutation that is amenable to migalastat in vitro) matches that in the NICE scope. The company's statement of the decision problem and the NICE scope do not mention that migalastat is expected to be indicated for people aged 16 years and older. However, the CS does limit its consideration of clinical evidence and its economic evaluation to patients aged over 16 years.

Intervention

At the time the ERG received the CS, migalastat was not licensed in the UK and had not been approved by the European Medicines Agency (EMA). According to the CS, a positive Committee for Medicinal Products for Human Use (CHMP) opinion was expected at the end of March 2016, with both full market authorisation and commercial product availability in the UK expected from June 2016. Subsequently, on 1 April 2016, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for migalastat, 'indicated for the long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-gal A deficiency) and who have an amenable mutation'.[16] Details of the licensed indication and relevant doses will be available in the final summary of product characteristics (SmPC). The CS states that the expected recommended dose is 1 capsule of 150 mg of migalastat hydrochloride (equivalent to 123 mg migalastat) once at the same time every other day. No dosage adjustment is required based on age (e.g. in the elderly) or in patients with hepatic impairment, but it is suggested that migalastat is not recommended for use in patients with Fabry disease who have a glomerular filtration rate (GFR) <30 mL/min/1.73 m^2. The company provided a confidential draft of the SmPC and the information reported in the CS is consistent with this.

Migalastat has currently not been reviewed by the Scottish Medicines Consortium, the All Wales Medicines Strategy Group, or the US Food and Drug Administration (FDA).

Comparators

The two comparators described in the CS (agalsidase alfa and agalsidase beta) are in line with the NICE scope and are currently used by the NHS for the treatment of patients with Fabry disease.

Agalsidase alfa (Replagal®, Shire Human Genetic Therapies AB; licensed in September 2002) is produced in a human cell line by gene activation and is indicated as a long-term enzyme replacement therapy for adults and children from the age of 7 years with confirmed diagnosis of Fabry disease. It is administered by intravenous infusion at 0.2 mg/kg body weight over approximately 40 minutes once every other week. One in 10 people according to the agalsidase alfa SmPC are affected by very common side effects, particularly general pain or discomfort.[17]

Agalsidase beta (Fabrazyme®, Genzyme Europe BV/Genzyme Corporation; licensed in December 2002) is produced in Chinese hamster ovary cells by recombinant techniques and is

indicated as a long-term enzyme replacement in adults, children and adolescents (aged 8 years and older) with a confirmed diagnosis of Fabry disease. It is administered by intravenous infusion once every other week at the recommended dose of 1.0 mg/kg body weight, with a recommended infusion rate of 15 mg/h, but the minimum infusion time should be at least 2 hours (generally requires 4 hours). According to the agalsidase beta SmPC, very common side effects (affecting one in 10 people) are: chills, fever, feeling cold, nausea, vomiting, headache and abnormal feelings in the skin such as burning or tingling. Dose adjustments may be required,[18] as may premedication with antihistamines, analgesics or corticosteroids.[19]

Outcomes

Outcomes stated in the final NICE scope match those addressed in the CS:

- Symptoms of Fabry disease (including pain)
- Gb3 levels in kidney
- Plasma lyso-Gb3 levels
- Kidney function
- Cardiac function and disease measurements (such as left ventricular mass index)
- Progression-free survival (time to occurrence of renal, cardiac, neurological and
- cerebrovascular events)
- Mortality
- Adverse effects of treatment
- Health-related quality of life (for patients and carers)

Further details about the outcomes reported in the CS are given below (see section 3.1.5~~3.1.5~~).

Economic analysis

As specified in the final NICE scope, the economic impact of migalastat therapy compared to ERT was analysed by the company in terms of its budget impact in the NHS and personal social services (PSS), and included costing and budget impact information, technical efficiency (the incremental benefit of the new technology compared to current treatment), productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used), and allocative efficiency (the impact of the new technology on the budget available for specialised commissioning). Outcomes were assessed over a lifetime horizon. The ERG's critique of the company's economic analysis is given in detail in section 4.

Other relevant factors

According to the CS, no issues relating to equity or equality are anticipated (CS page 26) and the ERG agrees that there appear to be no such issues. However, the treatment is limited to people with Fabry disease with a confirmed *GLA* mutation that is amenable to migalastat in vitro as per the licensed indication and is not available to children under 16 years of age.

There is currently no patient access scheme for migalastat.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's approach to systematic review

3.1.1 Description of the company's search strategy

A single overarching systematic search was conducted on the 7th December 2015 (reported in CS Appendix 1). The CS states that the systematic search was conducted to identify studies of interest reporting clinical efficacy and safety, HRQoL and economic evidence (CS page 72). The search strategy contains separate filters, linked to the disease area, covering the following:

- Cost Effectiveness (Economic filter)
- Health Related Quality of Life (Humanistic filter)
- Clinical Effectiveness (Clinical Efficacy and Safety Evidence Filter)

The search strategy was not limited by study design, so would capture both RCTs and non-randomised studies.

The selection of databases (Pubmed, Embase, Cochrane Library, DARE and Econlit) was adequate and the search strategies were comprehensive. Multiple search terms were grouped together on one long line for each search filter, which renders them harder to read and execute, and the numbers of references identified by each part of the search strategy are not provided. However, PRISMA flow charts are presented, indicating the total numbers of references identified for each systematic review. The Population was simply represented by "fabry" as a 'catch all' free text term, rather than being linked to migalastat or ERT. Grey Literature has been

covered by a good range of pertinent conference proceedings (ASN, ASHG, ACGM, ESHG, Fabry Neuropathy Update, ISPOR, LDN, SSIEM) and key clinical trial registers, with hand searching of reference lists.

The ERG ran searches on Medline, Medline in Process, Embase and the Cochrane Library to try and identify any new papers on migalastat and experimented with using the descriptor term "Fabry disease" and also "Anderson Fabry" free text. The company's own website was also checked for trials and the following ongoing trials databases were searched as a final check: UKCTG, ISRCTN, PROSPERO, Clinical Trials Registry.eu, and Clinicaltrials.gov. No relevant additional studies were found.

In summary, the searches in the submission are deemed to be fit for purpose and reproducible.

3.1.2 Inclusion/exclusion criteria used in the study selection

Inclusion and exclusion criteria are clearly tabulated and are the same for the identified published studies (CS Table C9.1 and pages 258-9) and unpublished studies (CS Table C9.2). The company has used one set of eligibility criteria to cover their systematic reviews of clinical effectiveness, HRQoL and economic evidence and also to identify evidence on safety. No specific criteria for separating the clinical, HRQoL, safety and economic studies are reported.

The eligibility criteria are consistent with the decision problem (CS Table A1.1), with some minor differences:

- Population: The company's decision problem specifies people with Fabry disease with a confirmed *GLA* mutation amenable to migalastat in vitro, but the inclusion criteria for the company's review do not mention the *GLA* mutation. The inclusion criteria specify that the population is 'adults', although no age cut-off is specified (as previously stated, migalastat is expected to be licensed for adolescents and adults aged ≥ 16 years when the marketing authorisation has been granted by the European Commission).
- Intervention and comparator: These are grouped together under the inclusion criterion "any/all pharmacological therapies aimed at primary treatment of Fabry disease".
- Outcomes: The inclusion criteria are generally broad and do not explicitly mention some of the outcomes listed in the decision problem (Fabry symptoms other than pain, Gb3 levels in kidney, lyso-Gb3 in plasma, or progression-free survival).

The company's eligibility criteria permitted a wide range of prospective and retrospective study designs to be included, covering RCTs and observational studies (including patient registries). The company excluded studies reporting switching between different types of ERT. Studies on a mixed population of patients with and without Fabry disease where outcomes were not reported separately for the Fabry patients were also excluded. The eligibility criteria did not restrict studies to any particular setting.

After checking the results of the searches, the ERG believes that the minor discrepancies between the company's eligibility criteria and decision problem would not have resulted in misclassification of any relevant or irrelevant studies. Overall the inclusion and exclusion criteria specified in the CS are consistent with the expected licensed indication and current NHS pathway for patients with Fabry disease. However, no explanation is provided in the CS of how safety data were selected from the search results. The adverse events reported in the CS are specifically taken from the ATTRACT and FACETS trials (CS section 9.7).

Study quality is not specified in the inclusion or exclusion criteria, other than stipulating a minimum sample size of 10 adults with Fabry disease. The CS does not discuss whether there might have been any bias in the study selection process.

The ERG notes that the company identified HRQoL outcomes from the review of clinical effectiveness and also from a review of HRQoL studies, but only the latter review provided HRQoL data for the company's economic analysis. Thus, HRQoL outcomes from the pivotal ATTRACT and FACETS RCTs reported in the clinical effectiveness section of the CS were not used in the economic analysis. PRISMA flow charts showing the numbers of studies excluded during the study selection process, with reasons for exclusion, are provided for the clinical effectiveness systematic review (CS Figure C9.1) the HRQoL systematic review (CS Figure C10.1) and the economic systematic review (CS Figure D11.1). The company's flow chart for the clinical effectiveness review is reproduced below in Figure 2.

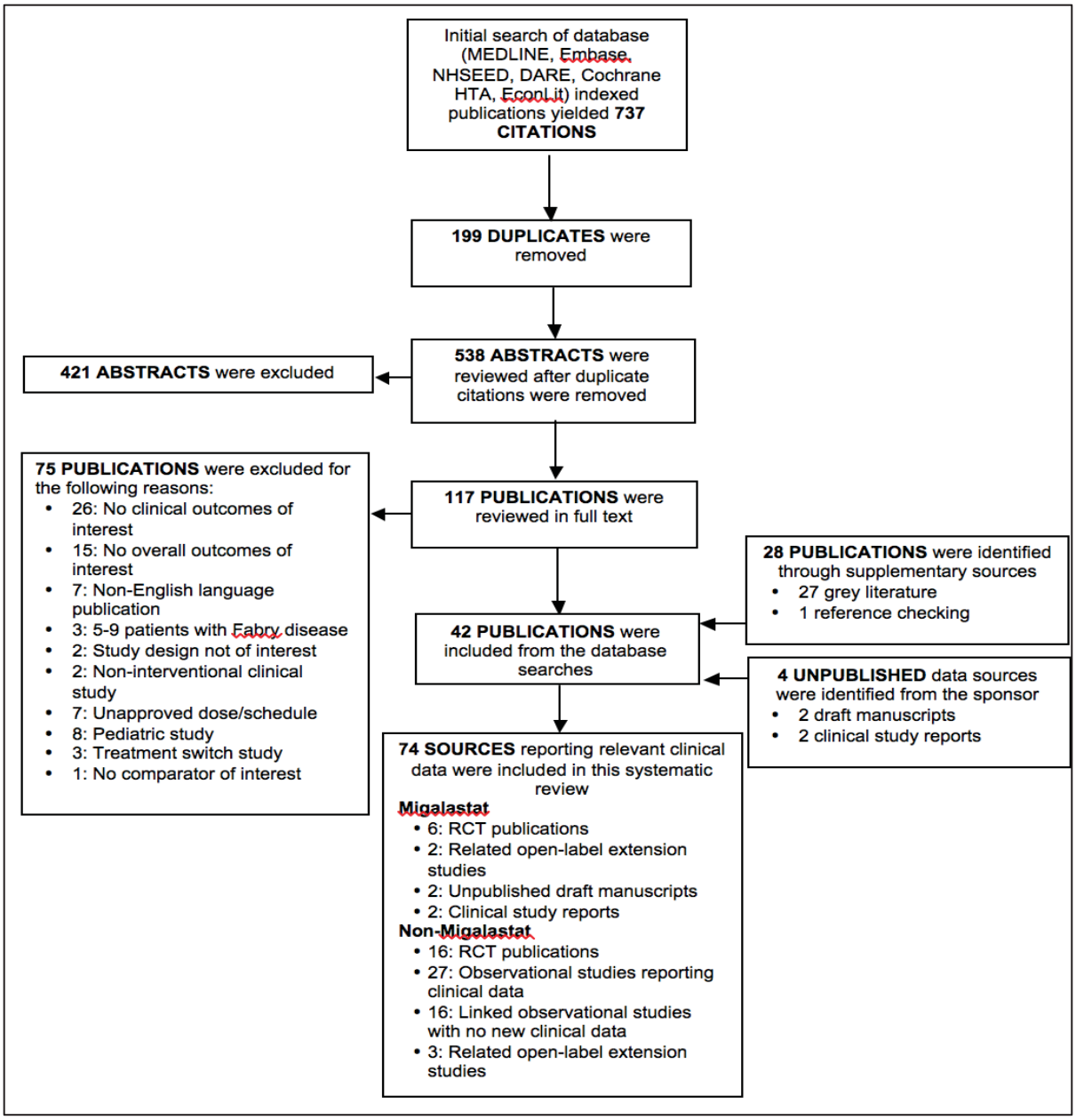

Figure 2 Study selection flow chart for the company's review of clinical effectiveness

3.1.3 Studies identified by the company

The company's searches identified 12 relevant documents on the clinical effectiveness of migalastat (Figure 2). The CS provides a list of these references (CS Table C9.6) and the company provided electronic copies of them. In response to a clarification request from the ERG and NICE (question A4), the company confirmed the identity of these references and provided a missing electronic copy of a conference abstract.

The 12 references report two pivotal phase 3 RCTs and two related phase 3 single-arm OLE studies, all of which were sponsored by the company and are currently unpublished. ATTRACT[20] was an 18-month open-label RCT, which randomised 60 patients who were receiving ERT to switch to migalastat (n=36) or to continue on ERT (n=24). After 18 months, patients from both arms of ATTRACT received migalastat for a further 18 months in the open-label extension (OLE) studies. FACETS[21] was a 6-month double-blind RCT, which randomised 67 patients to receive migalastat (n=34) or placebo (n=33). After 6 months, FACETS was unblinded and patients from both arms then received migalastat for a further 18 months in the OLE studies. The RCTs are described further below in section 3.1.3.1~~3.1.3.1~~ and the OLE studies are described in section 3.1.3.4~~3.1.3.4~~.

The 12 references identified in the company's searches are: the interim clinical study report (CSR) for ATTRACT;[22] the CSR for FACETS;[23] unpublished manuscripts reporting all the key outcomes in ATTRACT[20] and FACETS;[21] a conference paper reporting renal function in ATTRACT;[24] a conference paper reporting renal function, cardiac function, and HRQoL in ATTRACT;[25] a conference paper reporting biochemical outcomes in both ATTRACT and FACETS;[26] and five conference papers reporting combinations of renal function, cardiac function and/or HRQoL in the OLE studies following FACETS.[27-31] The ERG notes that an additional conference paper by Bichet and colleagues,[32] reporting renal and cardiac outcomes in the OLE period after ATTRACT, is not included in the list of 12 references but is cited elsewhere in the CS.

Of the two pivotal RCTs included in the company's review, only ATTRACT is directly relevant to the NICE scope. FACETS was a placebo-controlled RCT, but placebo is not a relevant comparator in the current appraisal, and results from ATTRACT, but not FACETS, were used by the company in their economic analysis (section 4). Given that there is a small evidence base for migalastat, the ERG has presented and critiqued both the ATTRACT and FACETS trials below.

3.1.3.1 Description of identified RCTs

The CS presents details of the studies' designs and methods for ATTRACT (CS Table C9.4) and FACETS (CS Table 9.5). ATTRACT was conducted at 25 study centres in 10 countries (six

European countries including the UK, plus Australia, Brazil, Japan and the US). According to the CS and CSR,[23] FACETS was conducted in 16 countries ([redacted], plus [redacted], Australia, [redacted] and the United States).

The eligibility criteria of the ATTRACT and FACETS RCTs are presented in the CS (Tables C9.4 and C9.5) and are reproduced below in Table 2~~Table 2~~ and Table 3~~Table 3~~. In both trials the eligible population was patients aged 16-74 years, who had been diagnosed with Fabry disease and had a confirmed *GLA* mutation responsive to migalastat in vitro. The eligibility criteria for both trials are consistent with the decision problem, although some patients in each trial were found, after randomisation, not to have a confirmed *GLA* mutation responsive to migalastat in vitro (see below).

Table 2 Inclusion criteria for the ATTRACT and FACETS trials

ATTRACT[20]	**FACETS**[21]
• Males or females aged between 16 and 74 years with Fabry disease diagnosis • Confirmed *GLA* mutation responsive to migalastat in vitro • ERT treatment for ≥12 months before visit 2 • ERT dose and regimen stable for 3 months and ≥80% of currently labelled dose and regimen for that time period • Estimated GFR ≥30 mL/min/1.73 m^2 • Any patients treated with ACEIs or ARBs on stable dose for ≥4 weeks before screening • Patients with reproductive potential were using medically accepted birth control methods for the duration of the study and for up to 30 days after the last study medication	• Males or females aged between 16 and 74 years with Fabry disease diagnosis • Confirmed *GLA* mutation responsive to migalastat in vitro • Naïve to ERT or had not received ERT for at least the 6 months before screening • Urine GL3 ≥ 4 times the upper limit of normal at screening • Any patients treated with ACEIs or ARBs on stable dose for ≥4 weeks before visit 1 • Patients with reproductive potential were using medically accepted birth control methods for the duration of the study and for up to 30 days after the last study medication

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; GFR: glomerular filtration rate

The ERG notes that the population of the ATTRACT trial excluded patients with ESRD and as such would not be reflective of patients with more severe Fabry disease. However, restricting

the population to those without ESRD is consistent with the draft SmPC, which states that migalastat is not recommended in patients with ESRD.

Table 3 Exclusion criteria for the ATTRACT and FACETS trials

ATTRACT [20]	FACETS [21]
• Kidney or any solid organ transplant, or scheduled for such transplant • Regular dialysis specifically for treatment of CKD • Transient ischemic attack, stroke, unstable angina, or myocardial infarction within 3 months before visit 1 • Clinically significant unstable cardiac disease (e.g., symptomatic arrhythmia, unstable angina, NYHA class III or IV congestive heart failure) • Pregnant or breast-feeding • History of allergy or sensitivity to study medication or excipients, or to other iminosugars such as miglustat or miglitol • Absolute contraindication to iohexol or inability to undergo iohexol GFR testing • Requires treatment with miglitol or miglustat • Received any investigational or experimental drug, biologic, or device within 30 days of visit 1 • Any condition or intercurrent illness that might prevent the patient from fulfilling protocol requirements or that might pose an unacceptable risk to the patient • Patient is unsuitable for the study in the opinion of the investigator	• Undergone or was scheduled to undergo kidney transplantation, or was currently on dialysis • eGFR < 30 mL/min/1.73m2 (CKD Stage 4 or 5) based on Modification of Diet in Renal Disease (MDRD) equation ($eGFR_{MDRD}$) at screening • Pregnant or breast-feeding • History of allergy or sensitivity to study drug (including excipients) or other iminosugars • Treated or had been treated with any investigational drug within 30 days of screening • Treated with migalastat at the time of study entry or had ever been treated with migalastat • Any inter-current condition or concomitant medication use considered to be an absolute contraindication to kidney biopsy or that could preclude accurate interpretation of study data • Otherwise unsuitable for the study, in the opinion of the investigator

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; NYHA: New York Heart Association

The primary and secondary outcomes of the trials are clearly stated in the CS (Tables C9.4 and C9.5). The ATTRACT trial specified two primary outcomes, which were changes in renal function assessed according to the measured and estimated GFR (mGFR and eGFR). These

are referred to as ‘co-primary’ outcomes. The primary outcome in the FACETS trial was a histological assessment of changes in kidney interstitial capillary inclusions of globotriaosylceramide (GL3).

Both trials included a range of secondary outcomes including renal function and renal events, cardiac function and cardiac events, cerebro-vascular events, and HRQoL. In some cases outcomes were classified as ‘tertiary or ‘exploratory’. Among the renal outcomes the company employed three methods for assessing the GFR: measurement using iohexol ($mGFR_{iohexol}$), and estimation using chronic kidney disease epidemiology criteria ($eGFR_{CKD\text{-}EPI}$) or Modified Diet in Renal Disease criteria ($eGFR_{MDRD}$). The outcomes are described further and discussed in detail below in section 3.1.5. For both trials the CS and trial publications do not provide any rationale for how primary outcomes differ from secondary or tertiary outcomes.

The CS reports that different populations were used for the primary efficacy analyses in ATTRACT and FACETS (CS pages 95-96). The analysis populations are described in more detail below (section 3.1.6~~3.1.6~~).

The CS briefly reports the statistical analysis approaches employed in the RCTs. These are described further and discussed in detail below (section 3.1.6). Non-inferiority analysis was not possible due to the small sample size a modified approach was used, which the CS (page 80) states was developed in conjunction with the EMA. Justification for the sample size is not provided for either trial.

Although the CS does not define any pre-specified subgroups, it states that analyses of subgroups for clinical efficacy were conducted in both trials (section 3.1.6~~3.1.6~~); however, results of these analyses, with minor exceptions, are not reported in the CS.

The numbers of participants who were screened for eligibility, randomised, and completed the RCTs and the subsequent OLE studies are clearly presented in the CS in CONSORT flow charts (CS Figures C9.5 and C9.6) and these are reproduced below in Figure 3~~Figure 3~~ and Figure 4~~Figure 4~~. The CONSORT flow chart for FACETS reported in the CS (Figure C9.6) contains errors, which were corrected by the company in response to a clarification request by the ERG and NICE (question A9). The corrected flow chart is shown in Figure 4~~Figure 4~~.

Note that the CONSORT flow chart for the FACETs RCT and OLE study (Figure 4~~Figure 4~~) classifies the study period into three stages: stage 1 (the RCT), stage 2, and the OLE, but this is not consistent with how the OLE studies are reported elsewhere in the CS. For clarification of how the OLE studies have been interpreted by the ERG see section 3.1.3.4~~3.1.3.4~~.

Figure 3 CONSORT flow chart for the ATTRACT RCT and OLE studies

Figure 4 CONSORT flow chart for the FACETS RCT and OLE studies

Eight patients (13%) withdrew from the ATTRACT RCT (labelled as 'discontinued') in Figure 3~~Figure 3~~. These were six patients in the ERT arm who all withdrew consent due to (unspecified) "logistical reasons"; and two patients in the migalastat arm, one of whom withdrew consent and one had depression. Three patients (4%) withdrew from the FACETS RCT, all of whom were in the placebo arm: two withdrew consent and one became pregnant. It is not clear which of these patients were classed as 'lost to follow up' and 'discontinued' in Figure 4~~Figure 4~~.The numbers of patients who completed the OLE studies following the RCTs were [redacted]* Reasons for withdrawal from the OLE studies are not reported.

Although the inclusion criteria specify patients should have had a confirmed *GLA* mutation responsive to migalastat in vitro,

[redacted] The CS explains that the classification of mutations changed after the patients were enrolled in the phase 3 RCTs as a result of the mutation assay being validated and updated (CS page 87). However, it is unclear why there is a difference between the ATTRACT and FACETS trials and also an imbalance between the study groups within FACETS in the proportions of patients who were found not to have amenable mutations.

The CS and also the unpublished manuscripts[20, 21] present population baseline characteristics differently for the ATTRACT and FACETS studies. ATTRACT baseline characteristics are presented for the safety population (CS Table C9.7), whilst those for FACETS are presented for the ITT population (CS Table C9.8). Those baseline characteristics which are reported for both the migalastat and comparator arms of each trial are reproduced below in Table 4~~Table 4~~ (demographic details and renal outcomes), Table 5~~Table 5~~ (HRQoL) and Table 6~~Table 6~~ (Fabry disease phenotype).

3.1.3.2 Baseline differences between the included trials

As shown in Table 4~~Table 4~~, Table 5~~Table 5~~ and Table 6~~Table 6~~, the baseline characteristics of the ATTRACT and FACETS trials differed a number of respects. These baseline differences between the trials are consistent with ATTRACT recruiting patients later in the disease process (according to the inclusion criteria, ATTRACT patients had received prior ERT whereas FACETS patients had not). Baseline HRQoL was not reported for the FACETS trial, either in the CS or the supporting manuscript,[21] so cannot be compared between the trials.

Table 4 Baseline population characteristics in the ATTRACT and FACETS trials

Characteristic	ATTRACT safety population		FACETS ITT population	
	Migalastat (n=36)	ERT (n=21)	Migalastat (n=34)	Placebo (n=33)
Age, years, mean±SE (range)	50.2±2.3	46.3±3.3	40 (16 to 68)	45 (24 to 64)
Female, %	56	57	65	64
Amenable *GLA* mutation, n (%)	34 (94)	19 (90)	28 (82)	22 (67)
Years since diagnosis, mean±SE	10.2±2	13.4±2.6	5.7±1.2	7.1±1.4
24-hour protein, mg/24 hr, mean±SE	267±69	360±150	342±79	452±109
% with 24-hour urinary protein ≥100 mg	58	57	NR	NR
$mGFR_{iohexol}$ (mL/min/1.73 m^2), mean±SE	82.4±3	83.6±5.2	83±5.3	86±4.3
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2), mean±SE	89.6±3.7	95.8±4.1	95±4.9	94±3.7
$eGFR_{MDRD}$ (mL/min/1.73 m^2), mean±SE	[redacted]	[redacted]	90±4.0	88±6.5
Prior ERT treatment, n (%)				
Agalsidase alfa	[redacted][a]	[redacted]	NR	NR
Agalsidase beta	[redacted][a]	[redacted]	NR	NR
Unspecified	NR	NR	5 (15)	12 (36)
Use of ACEI/ARB/RI, n (%)	16 (44)	11 (52)	6 (18)	13 (39)

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; NR: not reported; RI: renin inhibitor

[a] data for one patient are missing without explanation; unclear which ERT they received

Table 5 Baseline HRQoL in the ATTRACT trial

HRQoL measure	Migalastat (n=34)	ERT (n=16 for PCS, n=17 for MCS)[a]
SF-36 PCS score, mean±SE	[redacted]	[redacted]
SF-36 MCS score, mean±SE	[redacted]	[redacted]
BPI-pain severity score, mean±SE	[redacted]	[redacted]

MCS: Mental Component Summary; PCS: Physical Component Summary

[a] patients without missing data

Table 6 Fabry disease phenotypes in the ATTRACT and FACETS trials

Phenotype, n (%) in the amenable mutations population	Migalastat (n=34)	ERT (n=19)	Migalastat (n=28)	Placebo (n=22)
Classic	[redacted]	[redacted]	18 (64)	12 (55)
Non-classic	[redacted]	[redacted]	1 (4)	0 (0)
Both	[redacted]	[redacted]	1 (4)	2 (9)
Unclassified	[redacted]	[redacted]	8 (29)	8 (36)

The ERG notes that the course of Fabry disease is generally different in men and women. The clinical advisor to the ERG commented that progression is generally slower in women and that, based on the limited baseline information reported in the CS, the ATTRACT trial population does not appear to be severely affected by Fabry disease. However, the CS reports an analysis of baseline disease severity by sex which shows that in both studies the majority of both male and female patients had multi-organ involvement and suggests a reasonable disease burden for most patients.

3.1.3.3 Baseline differences between arms within the included trials

As can be seen in Table 4~~Table 4~~, there are a number of imbalances in the patients' baseline characteristics between the migalastat and comparator arms in each trial:

- Mean age differed between the arms in both trials. In ATTRACT the mean age was 4 years older in the migalastat arm than the ERT arm, whilst in FACETS the mean age was 5 years younger in the migalastat arm than the placebo arm.
- The proportion of patients who had an amenable *GLA* mutation was 15% higher in the migalastat arm than the placebo arm in FACETS.
- Patients in the migalastat arm had a shorter time since diagnosis than those in the comparator arm in both trials (mean 3.2 years shorter in ATTRACT, 1.4 years shorter in FACETS).
- The total urine protein collected over 24 hours was less in the migalastat arm than in the comparator arm for both trials (mean 93 mg less in ATTRACT, 110 mg less in FACETS).
- GFR values were generally similar across all the trial arms, with the exception that the estimates based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) criteria and Modification of Diet in Renal Disease (MDRD) criteria were [redacted] in

the migalastat arm than the ERT arm of the ATTRACT trial (mean $GFR_{CKD-EPI}$ 6.2 mL/min/1.73 m^2 [redacted]).

- In FACETS, a lower proportion of patients in the migalastat arm than the placebo arm had received prior ERT (15% versus 36%) and a lower proportion had received ACEI, ARB or renin inhibitors (18% versus 39%). The CS mentions these as 'major differences' (Table C9.12).

The number of patients with amenable mutations in the ERT arm of the ATTRACT trial shown in Figure 3~~Figure 3~~ differs from that reported in the baseline characteristics (ERG Table 4~~Table 4~~) (22 and 19 respectively). The ERG presumes this is because baseline characteristics in the ATTRACT trial are reported for the safety population.

Table 5~~Table 5~~ shows baseline HRQoL scores reported in the ATTRACT trial. The SF-36 scores are presented on a scale ranging from 0 (lowest or worst possible level of functioning) to 100 (highest or best possible level of functioning) whilst the BPI pain severity scores are on a scale of 0 (no pain) to 10 (maximum pain). The SF-36 scores indicate that physical and mental functioning were [redacted]. The CS points out that patients experienced [redacted]. Overall, the SF-36 and BPI scores suggest that at baseline, patients in the migalastat arm had [redacted] than those in the ERT arm, although it is unclear whether these differences would be clinically meaningful.

Table 6~~Table 6~~ shows the distribution of Fabry disease phenotypes across the study arms within the ATTRACT and FACETS trials. Due to the relatively large proportion of patients for which the phenotype was not classified [redacted] it is difficult to tell whether there are any phenotype imbalances between the study arms.

3.1.3.4 Description of identified OLE studies

The CS identifies two ongoing open-label single-arm extension studies which followed the ATTRACT and FACETS RCTs (CS pages 24-25). These are identified by the company as AT1001-041 and AT1001-042, and we refer to these respectively as study 041 and study 042.

In studies 041 and 042 patients received migalastat hydrochloride 150mg given once every 2 days. Patients in these studies were recruited from the completed ATTRACT and FACETS RCTs, and also from a phase 2 study, FAB-CL-205 (discussed further below). According to the CS, study 041 was terminated at an unspecified time "for administrative reasons". Participants from study 041 were eligible to continue in study 042.

There is considerable inconsistency in the CS in how these OLE studies are described. The CS states that study 041 was terminated (CS Table A4.1) and also ongoing (CS page 89). The CS also uses an inconsistent numbering system to identify different stages of the OLE studies following the FACETS RCT. Stage 1 refers to the FACETS RCT itself. After clarification from the company it is understood that Stage 2 refers to the first 6 months of the OLE following FACETS (i.e. months 7-12), with stage 3, when mentioned, referring to the last part of the OLE (i.e. months 13-24) (CS pages 115, 122 and CS Tables C9.5 and C9.28). The CS does not explain why the OLE has been divided into these time periods or whether they relate to the timing of studies 041 and 042.

The CS also states (CS page 98) that no data are yet available for study 042, and it further states (CS page 89) that as of 5th February 2016 two patients were receiving migalastat in study 041, and 76 patients were enrolled in study 042. However, the outcome data presented in the CS from the OLE (CS page 119) do not agree with either of these statements.

Clearly there is potential for confusion in interpreting the OLE studies based on the way they are described in the CS. However, the ERG suggests that since studies 041 and 042 were very similar, in that patients received the same migalastat therapy, it is not necessary to consider the specific issues of reporting in the CS mentioned above. To assist interpretation, a simplified representation of the ERG's understanding of the relationship between the studies is shown in Figure 5.

Note that although the CS mostly presents results from 18 months of the OLE period, the OLE is ongoing and limited data beyond 18 months of OLE are reported for selected renal and cardiac outcomes (CS pages 119-120), but with small or unclear sample sizes (see section 3.3.3~~3.3.3~~).

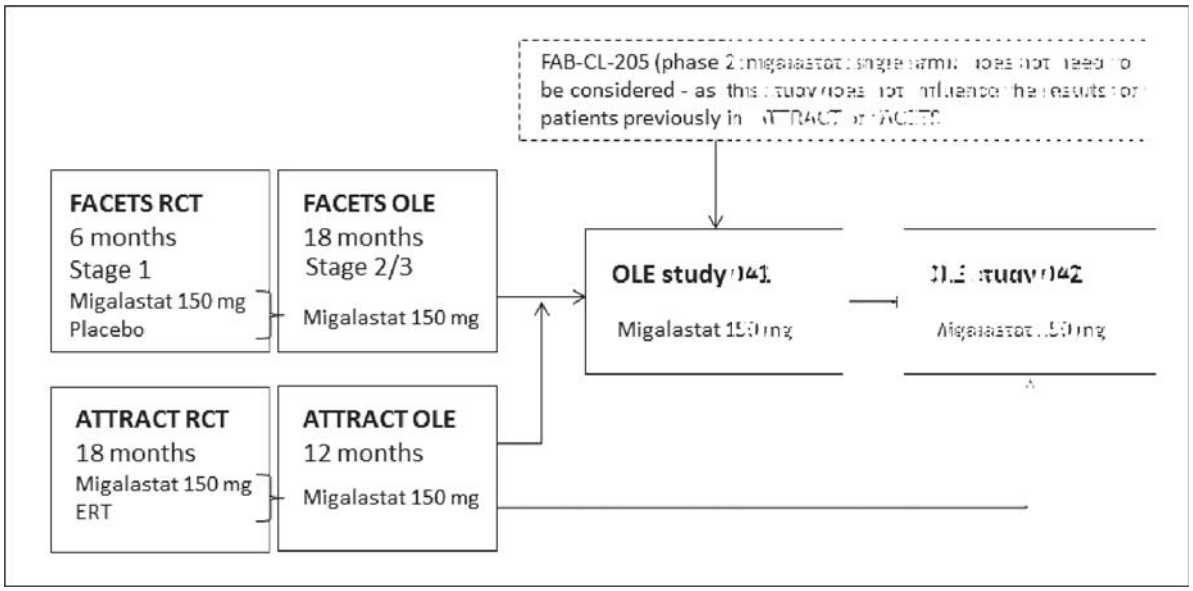

Figure 5 Summary of the relationship between the ATTRACT, FACETS and OLE studies

As shown in Figure 5, following completion of the 18-month randomised phase of ATTRACT patients from both arms were eligible to receive 12 months of migalastat therapy in the open-label phase. Following completion of the 6-month randomised phase of FACETS, patients from both arms were eligible to receive 18 months of migalastat therapy in the open-label phase. Patients from ATTRACT could therefore receive a total of 12 months of migalastat therapy (ERT → migalastat) or 30 months of migalastat therapy (migalastat → migalastat). Patients from FACETS could receive a total of 18 months of migalastat therapy (placebo → migalastat) or 24 months of migalastat therapy (migalastat → migalastat). At the end of the ATTRACT/FACETS open-label phases patients could continue to receive treatment with migalastat in the open-label extension studies 041 and 042. Outcomes in the OLE study period are reported separately in the CS for patients who originated from ATTRACT and FACETS, which means that the phase 2 study FAB-CL-205 has no influence on the OLE study results and therefore does not need to be considered (it is not discussed further in this report).

3.1.3.5 Ongoing trials

No relevant ongoing RCTs were identified by the ERG. However, the company is currently conducting an open-label 'physician initiated request' study (NCT01476163), in which physicians may request permission to treat specific adult patients with migalastat. Adult patients (aged 18-74 years) must have an amenable α-Gal A mutation, not meet eligibility criteria for existing migalastat clinical studies, and be unsuitable for or unable to access ERT.

Treatment is for up to 20 patients for 6 months with renewal every 6 months. The primary outcome measure is serious adverse events and reports of pregnancy. The study is expected to complete in October 2016.

3.1.4 Description and critique of the approach to validity assessment

The CS critically appraised both of the included trials, using Centre for Reviews and Dissemination (CRD) criteria as recommended by NICE. As shown below (Table 7~~Table 7~~), there are some differences between the judgements made by the company and the ERG concerning the quality of the RCTs.

Table 7 Company and ERG assessments of trial quality

Critical appraisal criterion	**Judgement**			
	ATTRACT		**FACETS**	
1. Was the method used to generate random allocations adequate?	**CS:**	Yes	**CS:**	Yes
	ERG:	Unclear	**ERG:**	Unclear
Comment: The randomisation methods were not explicitly stated. The company confirmed in their clarification response (question A5) that central randomisation was carried out by an external contractor in both trials. The ATTRACT trial stratified patients by gender and by a dichotomous classification of proteinuria; the FACETS trial stratified patients by gender only. A block randomisation procedure was used in both trials but with no indication of the number or size of blocks or how these related to the stratification factors. Selection bias might have been introduced if block sizes were small.				
2. Was the allocation adequately concealed?	**CS:**	N/A	**CS:**	Yes
	ERG:	Unclear	**ERG:**	Unclear
Comment: The CS provides judgements based on arguments about blinding rather than allocation concealment. The ERG and NICE therefore requested clarification about the company's approach to allocation concealment. The response received from the company (question A6) only mentions that an interactive voice response system was somehow involved, without any explanation of code concealment. In addition, it is unclear if block sizes were fixed, which potentially could make the allocation of participants predictable (selection bias).				
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	**CS:**	Yes	**CS:**	Yes
	ERG:	No	**ERG:**	No
Comment: ATTRACT: The CS and the unpublished manuscript[20] state that baseline characteristics were balanced between the migalastat and ERT groups. FACETS: The CS states the baseline characteristics were balanced between the migalastat and placebo groups, but also reports two major differences between the groups in the quality assessment of the trial (ACEI/ARB/ renin inhibitor use, and prior ERT). The ERG's view is that there were clear imbalances in several prognostic baseline characteristics in both RCTs between the migalastat and comparator groups, including differences in patients' age, time since diagnosis, and 24-hour urine protein (see section 3.1.3.3~~3.1.3.3~~ for details).				

continued

Table 7 – continued

Critical appraisal criterion	Judgement			
	ATTRACT		FACETS	
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	**CS:**	No	**CS:**	Yes
	ERG:	No	**ERG:**	Yes
Comment: ATTRACT: Open label. All outcomes would have high risk of performance bias and detection bias as patients, investigators and outcome assessors would have known the treatment allocation. A possible exception (unclear risk of detection bias) is for assessment of echocardiographic parameters, which the CS states was conducted through blinded, centralised evaluation, but the CS does not describe the method of blinding. FACETS: Double-blind, placebo-controlled. [redacted]Risk of detection bias is unclear since the methods of blinding outcome assessors are not reported ([redacted][21])				
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	**CS:**	Yes	**CS:**	Yes
	ERG:	Yes	**ERG:**	Yes
Comment: The company judged there to be imbalances in drop-outs between the groups [ATTRACT: migalastat 6% (n= 2) vs ERT 25% (n= 6); FACETS: migalastat 0% (n=0), placebo 9% (n= 3)]. However, in both RCTs the CS states that no adjustment for differences in drop-outs between the groups was needed. The risk of attrition bias is unclear since the CS does not report reasons for the dropouts in either RCT (i.e. it is unclear whether the dropouts would have altered the prognosis of the study groups). The fact that 25% of the patients receiving ERT in ATTRACT dropped out is of concern given the already small sample size (24 patients).				
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	**CS:**	No	**CS:**	No
	ERG:	Unclear	**ERG:**	Unclear
Comment: ATTRACT: Mitral valve ratios and peak inflow velocity were measured but not reported. Measures of functional diastolic and systolic grade were not specified as being measured but their results are reported. FACETS: Only some components of the SF-36 and GSRS HRQoL measures were reported. Several outcomes in both trials were reported only narratively (Section 3.3). Overall, the risk of selection bias in both trials appears low for the primary outcomes, but high for the patient-reported outcomes.				

continued

Table 7 – continued

Critical appraisal criterion	Judgement			
	ATTRACT		FACETS	
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?*	**CS:**	Yes	**CS:**	Yes
	ERG:	Yes	**ERG:**	Yes
Comment: * The CS only provides a general 'Yes' answer, which does not fully address all three parts of this question. The ERG interpretation is that (1) ITT analyses (i.e. all randomised patients) were conducted in ATTRACT for mGFR and eGFR (primary outcomes); and in FACETS for GL3 inclusions (primary outcome), mGFR and eGFR (secondary outcomes). (2) Although ITT analyses were appropriate, the primary focus in both RCTs was on modified ITT analyses that did not utilise all randomised patients. (3) Apart from AE in ATTRACT, missing data were not appropriately accounted for (in ATTRACT, [redacted] 3.1.6****** The CS does not specify how missing data were handled in FACETS).				

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

3.1.5 Description and critique of the company's outcome selection

The company's selection of outcomes is appropriate and consistent with the decision problem and NICE scope. The outcomes cover primarily the renal and cardiac manifestations of Fabry disease, and its effects on lipid biochemistry and on patients' HRQoL and safety. There do not appear to be any key outcomes that are missing, with the possible exception that a wider range of patient-reported HRQoL measures might have been helpful, given that Fabry disease can substantially affect patients' HRQoL. However, with the exception of adverse events, the outcomes reported in the clinical effectiveness section of the CS do not directly inform the company's economic evaluation (section 4).

The outcomes are divided into primary and secondary outcomes; and, in FACETS, some histological and HRQoL outcomes are referred to as 'tertiary' (CS Table C9.19). No rationale is given for this primary/secondary/tertiary classification of outcomes, i.e. it is not clear that the primary outcomes were statistically powered, since inadequate information was provided on sample size calculations in relation to statistical power (section 3.1.63.1.6).

The final outcomes reported in ATTRACT and FACETS can be divided into renal function, cardiac function, HRQoL, and safety. These outcomes are clinically appropriate as they capture aspects of Fabry disease morbidity that reflect how patients feel and/or are used in clinical decision-making (CS Tables B8.2 and B8.3). The trials also reported biochemical outcomes of GL3 and plasma lyso-Gb3 distributions, and activity of the enzyme α-gal A, which are primarily indicators of migalastat efficacy. These biochemical outcomes would be expected to correlate generally with migalastat efficacy and disease severity, but may not directly reflect patients' symptoms and (as indicated in in CS Table B8.3) do not themselves have a clear role in clinical decision making.

The ATTRACT trial had two primary outcomes for assessing renal function based on two methods for determining the annualised change in GFR. The GFR is a widely-used and clinically relevant means of assessing renal function and specific thresholds of the GFR are used in clinical practice to identify patients with different stages of kidney failure. GFR is also relevant to migalastat therapy since the draft SmPC states that migalastat is not recommended for patients with Fabry disease who have GFR less than 30 mL/min/1.73m^2 (this limitation does not apply to ERT which, unlike migalastat, are not renally excreted).

The primary outcome in the FACETS trial was histology assessment to determine changes in kidney interstitial capillary inclusions of GL3. This is a relevant biochemical outcome, since in Fabry disease the accumulation of GL3 within cells leads to cellular damage and progressive and irreversible organ damage.

As a relatively large number of outcomes is reported, the key features of these are summarised in Table 8~~Table 8~~.

3.1.5.1 Renal outcomes

The renal outcomes assessed were measured GFR, estimated GFR (based on two methods), and the total amounts of protein, albumin and creatinine in the urine collected over a 24-hour period. Previous research has suggested that estimated and measured changes in GFR may not always concur, [33] and so it is appropriate that the measured $GFR_{iohexol}$ was employed in addition to the estimated GFR outcomes in both trials.

Table 8 Summary of clinical outcomes reported in ATTRACT and FACETS trials

Outcome	Description	ATTRACT	FACETS
Renal function			
$mGFR_{iohexol}$	GFR measured by assessing plasma concentrations of intravenously-injected iohexol.	Primary	Secondary
$eGFR_{CKD-EPI}$	GFR estimated from serum creatinine using Chronic Kidney Disease Epidemiology (CKD-EPI) criteria.	Primary	Secondary
$eGFR_{MDRD}$	GFR estimated from serum creatinine using Modification of Diet in Renal Disease (MDRD) criteria.	Secondary	Secondary
24-h urine protein	Proteinuria: indicator of kidney dysfunction.	Secondary	Secondary
24-h urine albumin	Microalbuminuria: early indicator of kidney dysfunction.	Secondary	Secondary
24-h urine creatinine	Creatinine clearance: indicator of kidney dysfunction.	Secondary	Secondary
Cardiac function			
ECHO LVMI	Echocardiographic measurement of left ventricular mass index	Secondary	Tertiary
ECHO LVEF	Echocardiographic measurement of left ventricular ejection fraction and LV diameter fractional shortening	Secondary	Not assessed
ECHO LVPWT	Echocardiographic measurement of left ventricular posterior wall thickness diastolic	Secondary	Not assessed
ECHO IVSWT	Echocardiographic measurement of intra-ventricular septal wall thickness diastolic	Secondary	Not assessed
Mitral flow velocity and valve ratio	Pulsed-wave Doppler measurement of peak inflow for specified valve criteria	Secondary but NR	Not assessed
Composite clinical outcome			
Composite clinical outcome	Specified criteria for: eGFR, urine protein; cardiac events; cerebrovascular events; or death	Secondary	Not assessed
HRQoL			
SF-36 PCS	SF-36 Physical Component Summary	Secondary	Secondary
SF-36 MCS	SF-36 Mental Component Summary	Secondary	Secondary
BPI Short Form	BPI Pain severity component	Secondary	Secondary
GSRS	Gastrointestinal Symptoms Rating Scale	Not assessed	Secondary[a]

continued

Table 8 - continued

Biochemical outcomes			
Kidney interstitial GL3 inclusions	Histologically-assessed indication of migalastat effect on GL3 distribution	Secondary	Primary = ≥50% reduction[b]
Urine GL3	As above	Not assessed	Secondary
Plasma lyso-Gb3	Plasma-assessed indication of migalastat effect on lyso-Gb3 distribution	Not assessed	Secondary[c]
PBMC α-gal A activity	Outcome indicating migalastat efficacy at promoting alfa-Gal A activity	Secondary	Exploratory

BPI: Brief Pain Inventory; NR: not reported; TIA: transient ischaemic attack; PBMC: peripheral blood mononuclear cell; WBC: white blood cell.
[a] specified in CS as both a secondary and tertiary outcome
[b] secondary and tertiary outcomes were also specified for interstitial GL3 inclusions
[c] specified in CS as both a secondary and exploratory outcome

As mentioned in the CS (page 34), microalbuminuria, proteinuria and elevated serum creatinine levels (used in estimation of GFR) are respective indicators of the stages of kidney disease, and the urinary protein to creatinine ratio is predictive of renal disease progression. In ATTRACT the urine albumin and creatinine were reported only as the abumin:creatinine ratio whereas in FACETS albumin and creatinine were reported separately without the ratio (results section 3.3.1.13~~.3.1.1~~). Renal impairment is indicated when the urine protein exceeds 100 mg/day or when the albumin:creatinine ratio is at least 2.5 mg/nmol for males or 3.5 ng/nmol for females.

3.1.5.2 Cardiac outcomes

The cardiac outcomes assessed are mainly related to the cardiac hypertrophy experienced in Fabry disease: left ventricular mass index (LVMI), ejection fraction (LVEF), fractional shortening at diastole, and posterior wall thickness (LVPWT); and the intra-ventricular septal wall thickness (IVSWT). Only the LVMI was measured in FACETS. The CS states that in ATTRACT measurements were made of mitral valve ratios and peak inflow velocity, but no results for these are provided in the CS, manuscript[20] or interim CSR. [22] The CS (page 107) does not explicitly state that 'functional diastolic and systolic grade' outcomes were measured, but does mention (narratively only) results for these outcomes (results section 3.33~~.3~~). According to the ATTRACT interim CSR, [22] diastolic grade was classified as [redacted] (CSR Table 14.2.6.5.1-1) whilst systolic grade was

classified as [redacted](CSR Table 14.2.6.6.1-1), but no definitions of these classes are given.

3.1.5.3 Composite clinical outcome

In the ATTRACT trial, a composite clinical outcome was employed, comprising pre-specified renal, cardiac and cerebrovascular outcomes. This composite outcome does not appear to be used directly for clinical decision-making in Fabry disease management (CS Table B8.3) and its main purpose (not stated in the CS) seems to be to enable differences between migalastat and ERT therapy to be detected given that the sample size is relatively small and individual renal, cardiac and cerebrovascular events are relatively uncommon. The CS also reports the constituent renal, cardiac and cerebrovascular components of the composite outcome separately (results section 3.3.1.3~~3.3.1.3~~).

3.1.5.4 HRQoL

Both ATTRACT and FACETS assessed HRQoL using the SF-36 Physical Component Summary (0-100 scale) and the Brief Pain Inventory (BPI) short form (0-10 scale). In addition, ATTRACT reported the SF-36 Mental Component Summary (0-100 scale), whilst FACETS employed the Gastrointestinal Symptoms Rating Scale (GSRS).

3.1.5.5 Biochemical outcomes

FACETS, but not ATTRACT, assessed inclusions of GL3 in kidney interstitial capillaries. As noted above, the primary outcome in FACETS was the percentage of patients who had at least 50% reduction in the mean number of inclusions from baseline to 6 months. FACETS also assessed changes in GL3 inclusions in other kidney cell types (podocytes, endothelial cells, mesangial cells) and changes in urine GL3. Both ATTRACT and FACETS trials assessed changes in the concentration of plasma lyso-Gb3. In addition to the GL3 and lyso-Gb3 outcomes, which assess downstream effects of α-gal A activity, the activity of the α-gal A enzyme itself was also measured in peripheral blood mononuclear cells and is reported for males in both trials.

3.1.5.6 Adverse events

Safety outcomes reported in the ATTRACT and FACETS trials are serious adverse events (SAE), treatment-emergent adverse events (TEAE) and discontinuations due to adverse events. The CS and unpublished manuscripts do not define SAE and TEAE. The definitions given in the CSRs are shown in Table 9~~Table 9~~. In FACETS, TEAE are defined according to the study

stage, where Stage 1 refers to the FACETS trial and Stage 2 refers to the OLE period. In the context of adverse events reporting 'Stage 2' refers to the 7-12 month OLE period.

Table 9 Definitions of adverse events in the ATTRACT and FACETS trials

	ATTRACT	FACETS
SAE	[redacted] (interim CSR page 33).	[redacted] (CSR page 44).
TEAE	[redacted] (interim CSR page 44).	[redacted] (CSR page 59).

SAE: serious adverse event; TEAE: treatment-emergent adverse event

3.1.6 Description and critique of the company's approach to trial statistics

Sample size calculations

Justification for the sample size is not mentioned in the CS or the supporting manuscripts for either trial.[20, 21] The only sample size calculation reported is in the FACETS CSR, [23] which provides a justification [redacted] However, the intended power is not clear [redacted]

Subgroups

Although the CS does not define any pre-specified subgroups, it states that analyses of subgroups for clinical efficacy were conducted in both trials (CS section 9.4.4). In ATTRACT the subgroups were sex and proteinuria (< 100 mg/24 h; ≥ 100 mg/24 h). The CS states that in FACETS [redacted]. However, results of these analyses, with a few exceptions, are not reported in the CS (see section 3.33.3).

3.1.6.1 Analysis populations

The CS (page 87) explains that for patients to be enrolled in ATTRACT or FACETS they were required to have an amenable mutation, defined as a mutation giving a relative increase in α-Gal A activity ≥1.2 fold above baseline with an absolute increase of ≥3% after incubation with 10 μM migalastat. Following the commencement of the ATTRACT and FACETS trials, some changes were made to the mutation assay during a validation process. As a result, when patients in these trials were tested with the validated assay (referred to by the company as the Migalastat Amenability Assay), some were reclassified from having amenable to non-amenable mutations. Overall, 12% of patients randomised to ATTRACT (7/60) and 25% randomised to FACETS (17/67) were found after randomisation to have non-amenable mutations.

In both trials an intention to treat (ITT) analysis (i.e. including all randomised patients) was planned for the primary efficacy outcomes. However, the CS states that this was not considered

to be the most appropriate analysis due to the changes in the protocol for identifying amenable mutations.

In ATTRACT, all outcome analyses (except HRQoL) were based on what the company refers to as the 'modified ITT' population (mITT). This is defined in the CS as randomised patients with amenable mutations receiving at least 1 dose of study drug and having baseline and post-baseline $mGFR_{iohexol}$ and $eGFR_{CKD-EPI}$ measures. However, the term "mITT" as employed in the ATTRACT trial is misleading since this is effectively a per protocol population. ITT analysis results for the co-primary outcomes in ATTRACT are presented in the CS alongside the mITT analyses. In the migalastat arm the ITT population and the mITT population had 36 and 34 patients respectively whereas in the ERT arm the corresponding numbers were 24 and 18 (CS Table C9.11) (note that CS Table C9.11 incorrectly states 34 were randomised to migalastat – the correct number is 36). The CS also defines a separate per protocol population for ATTRACT (patients from the modified ITT population who completed the 18-month treatment period and who did not have a change in the use of ACEI, ARB, or renin inhibitors).

In FACETS, post-hoc analysis was carried out for patients in the ITT population who had amenable mutations based on the Migalastat Amenability Assay (referred to as the 'amenable mutations population'). For the primary outcome and some (but not all) of the secondary outcomes in FACETS, ITT analysis results are presented alongside the amenable mutations analysis results. The amenable mutations population was defined before FACETS was unblinded.

3.1.6.2 Statistical approaches in ATTRACT

The CS states that a standard non-inferiority analysis comparing migalastat and ERT on the co-primary (GFR) endpoints in the ATTRACT trial was not possible due to the small sample size. The ERG agrees that the required sample size for detecting non-inferiority[34] would not be achieved with the small available population of Fabry patients. Pre-specified criteria were therefore developed by the company in conjunction with the EMA to define comparability of GFR results for migalastat and ERT. Based on these criteria, migalastat would be considered comparable to ERT if both of the following occurred:

- The difference between the means for the annualised change in GFR between migalastat and ERT was ≤2.2 mL/min/1.73 m^2/year

- The overlap in the 95% confidence intervals (CIs) for these means was >50%

However, no justification for these criteria is given in the CS, the ATTRACT trial manuscript,[20] the interim CSR,[22] or the draft European Public Assessment Report (EPAR).[35]

Statistical analysis of the co-primary outcomes in ATTRACT employed analysis of covariance (ANCOVA) with the following factors and covariates: treatment group, sex, age, baseline GFR ($mGFR_{iohexol}$ or $eGFR_{CKD\text{-}EPI}$) and baseline 24-hour urine protein. Annualised changes in GFR were calculated using linear regression slopes. ANCOVA was also employed for analysing the echocardiographic outcomes (LVMI, LVEF, LVPWT, IVSWT) and the composite clinical outcome, but the CS does not state whether the same covariates were employed as for the primary outcome analyses. Formal statistical analysis was not reported in the CS for 24-hour urine protein, the 24-hour albumin: creatinine ratio, HRQoL outcomes (SF-36 and BPI) or biochemical outcomes (plasma lyso-Gb3, α-Gal A activity). According to the Interim CSR,

[redacted]*Ac

counting for missing data in ATTRACT

The CS states that for the ATTRACT trial

[redacted]

The CS does not specifically report how missing HRQoL data were handled. The number of missing data in ATTRACT compared to the sample size expected for the mITT analysis ranged from 0% to 11% depending upon the HRQoL outcome (see results, section 3.3.1.5~~3.3.1.5~~).

Analysis reporting in ATTRACT

Results of the statistical analyses in the ATTRACT trial are reported in the CS as means or medians separately for the migalastat and ERT groups for all outcomes, with limited presentation of differences between the migalastat and ERT groups and no formal consideration of effect sizes. An exception is that analysis results for the echocardiographic outcomes LVPWT and IVSWT are only reported narratively. There is considerable inconsistency between the outcomes as to whether standard deviations, standard errors, 95% CI and/or p-values are reported (CS Table C9.13).

3.1.6.3 Statistical approaches in FACETS

The primary outcome in FACETS (% of patients with a ≥50% reduction in GL-3 inclusions per interstitial capillary) and also the secondary outcome of change in mean GL-3 inclusions per interstitial capillary were analysed using Cochran Mantel Haenszel tests. The remaining efficacy outcomes in the FACETS trial were analysed using ANCOVA. However, the factors and covariates specified in the ANCOVA were different for each outcome analysed and the CS does not explain this:

- For analysing the change in the percentage of interstitial capillaries with zero GL3 inclusions, the ANCOVA was adjusted for baseline value and factors for treatment group, sex, and the treatment by baseline interaction, sex by treatment interaction and sex by baseline interaction.
- For analysing median percentage change from baseline in interstitial capillary GL3 inclusions, the ANCOVA included baseline value and sex as covariates.
- For analysing GFR outcomes, factors and covariates in the ANCOVA were: treatment group, sex, age, baseline GFR (mGFRiohexol or $eGFR_{CKD\text{-}EPI}$) and baseline 24-hour urine protein.
- For analysis of plasma lyso-Gb3 (stated as being an exploratory analysis) ANCOVA included treatment as a factor with the baseline value as a covariate and the treatment by baseline interaction.

The CS does not report which covariates were included in the ANCOVA for the urine GL3 outcome or Gastrointestinal Symptoms Rating Scale HRQoL outcome, and does not specify the statistical analysis methods employed for analysing other HRQoL outcomes (BPI, SF-36) or echocardiographic assessments (LVMI). For GFR outcomes, annualised changes were

calculated using linear regression slopes. According to the CSR,
[redacted]

Accounting for missing data in FACETS

For the FACETS trial the CS states that since no dropouts occurred data were available for all patients (CS Table C9.12). However, as shown in the CONSORT flow diagram, there were 3 dropouts (ERG Figure 4~~Figure 4~~). The ERG notes that, in addition to the dropouts shown in the CONSORT flow diagram, other data may have been missing, for example if not all patients provided HRQoL measurements. The CS does not report sample sizes for the HRQoL outcomes in FACETS (section 3.3.2.4~~3.3.2.4~~) and so the extent of missing HRQoL data is unclear.

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Analysis reporting in FACETS

Mean differences (with 95% CI) between migalastat and placebo are reported for the outcomes relating to interstitial capillary inclusions of GL3 and for the exploratory lyso-Gb3 outcome. For the other outcomes means or medians are reported for each study group (i.e. migalastat or placebo) but not for the difference between groups. Exceptions are the results for the echocardiographic outcome LVMI and the HRQoL outcomes BPI and SF-36 which are only reported narratively. There is considerable inconsistency between the outcomes as to whether standard deviations, standard errors, 95% CI and/or p-values are reported (CS Table C9.14).

3.1.6.4 Summary of the company's statistical analysis approaches

Overall, the statistical analysis methods appear to have been reasonable. However, the ERG has some concerns relating to the analysis populations and the way the statistical analysis results are presented:

- As acknowledged in the CS, due to small sample sizes it was not possible to formally test noninferiority of migalastat compared to ERT for renal function.
- No justification is given in the CS for the criteria employed by the company for deciding whether GFR outcomes were 'comparable' between migalastat and ERT.
- It is unclear why the populations for analysis with amenable mutations were defined differently in each trial. In ATTRACT, the 'modified ITT' population was effectively a per protocol population. In FACETS, although the amenable mutations population was

based on the numbers randomised who had eligible mutations, in practice this had 25% fewer patients than the randomised population.

- Missing data for the primary outcomes were not taken into account.
- For HRQoL outcomes the analysed sample size was smaller than the mITT analysis sample size due to missing data; the number of missing HRQoL data in FACETS was not reported.
- It is unclear why different sets of covariates or explanatory factors appear to have been used in the ANCOVA models for each outcome in the FACETS trial.
- The company has not considered the potential implications of conducting multiple statistical tests in ATTRACT and FACETS and has not made any adjustments for this.

3.1.7 Description and critique of the company's approach to the evidence synthesis

A narrative review of the various included studies is provided. Results are reported in tables, charts and text. The narrative generally reflects the data in the included studies. However, the CS gives limited discussion of the clinical outcomes and does not mention what the company considers to be clinically meaningful differences in the primary outcomes.

As there were only two included RCTs which had different comparator groups, no meta-analysis was conducted.

Based on a feasibility study conducted by an external contractor,[36] the company concluded that no credible NMA 'could be conducted for migalastat in patients with Fabry disease for key outcomes'. The company provided the ERG with a copy of the confidential network NMA feasibility report.[36] Six RCTs were included, comparing migalastat or ERT to placebo. The CS provides tables indicating key differences between these RCTs in outcomes (CS Table C9.29, page 126) and population characteristics (Table C9.30, page 127). An overview of these six RCTs which the company considered for NMA is provided below (Table 10).

The NMA feasibility study concluded that although hypothetical networks could be formed with the trials, the outcomes and populations were too inconsistent between the trials to enable comparisons (Table 10). The CS states (page 126) that it was not feasible to compare adverse events across the trials due to differences in how such events were reported and the fact that most trials failed to report what definitions of adverse events they used. The ERG agrees with

the conclusion of the report that, due to the heterogeneity of the outcomes and highlighted differences in the trials' patient baseline characteristics, a NMA would be inappropriate.

Table 10 Overview of RCTs considered by the company for NMA

RCT name & duration	Population (with Fabry disease)	Comparators	Outcomes common to all trial arms
ATTRACT[20] 18 months	60 adult patients with prior ERT treatment, eGFR ≥30 mL/min/1.73 m2	Migalastat vs ERT	• GFR • LVMI • GL3 levels in urine samples • HRQoL (SF36) • Pain (BPI) • Progression –free survival
FACETS[21] 6 months	67 adults naïve to ERT or not ERT for ≥6 months before screening, urine GL3 ≥ 4 x ULN	Migalastat vs Placebo	• GL3 levels in kidney samples • GL3 levels in urine samples • GFR • LVMI • HRQoL (SF36) • Pain (BPI)
AGAL-008-00[37] 18 months	82 adults with mild to moderate kidney disease	ERT vs Placebo	• Time to death • Progression –free survival
AGAL-1-002-98[38] *20 weeks	58 adults with a activity level of α-gal A ≤1.5 nmol/hour/ml in plasma or <4 nmol/hour/mg in leukocytes	ERT vs Placebo	• HRQoL (SF36)
TKT 007[39] 6 months	15 adult hemizygous male patients with evidence of increased LVM and two-dimensional echocardiography	ERT vs Placebo	• GL3 levels in urine samples • LVM (can be converted to LVMI)
Not reported[40] 6 months	26 adult hemizygous male patients with neuropathic pain	ERT vs Placebo	• GL3 levels in kidney samples • GL3 levels in urine samples • GFR • HRQoL • Pain (BPI)

BPI, Brief Pain Inventory; GL3, globotriaosylceramide; eGFR, GFR, glomerular filtration rate; LVM, left ventricular mass; LVMI, left ventricular mass index; ULN, upper limits of normal; OLE, open label extension; SF-36, Short Form 36 Health survey.

3.2 Summary statement of the company's approach

The ERG considers that the clinical evidence presented in the CS was assembled in an appropriate manner (Table 11~~Table 11~~). However, the CS critique of the included studies differs

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in several respects from that of the ERG. In particular, the ERG identified risks of selection, performance and detection biases in the included RCTs (see Table 7), which the CS does not mention. The processes employed by the company for screening and data extraction reported in the CS were adequate. Inclusion/exclusion screening at both the title/abstract and full text stages was conducted independently by two 'investigators', while data extractions were completed by a single researcher and checked by a second using a piloted data extraction form (CS page 260). In response to a clarification request by the ERG and NICE (question A7), the company confirmed that quality assessment of the included studies was conducted by one reviewer and checked by a second reviewer.

The submitted evidence generally reflects the decision problem defined in the CS.

Table 11 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes (inclusion/exclusion criteria are clearly tabulated for both studies)
2. Is there evidence of a substantial effort to search for all relevant research (i.e. all studies identified)?	Yes (searches in the submission are deemed to be fit for purpose and reproducible)
3. Is the validity of included studies adequately assessed?	Uncertain. There are differences between the CS and the ERG assessment, mostly due to insufficient information reported in the CS.
4. Is sufficient detail of the individual studies presented?	Yes, except sample sizes are not reported for some outcomes
5. Are the primary studies summarised appropriately?	Yes (although outcomes are presented in an inconsistent order which is difficult to follow)

3.3 Presentation and critique of clinical evidence submitted by the company

This section summarises the clinical effectiveness and safety outcomes presented in the CS. Although a range of outcomes is provided by the CS for the ATTRACT and FACETS trials, only information from ATTRACT is directly relevant to the NICE scope and is employed by the company in their economic analysis (section 4). However, given that there is a small evidence

base for the clinical effectiveness of migalastat, the full results from ATTRACT and FACETS as well as the OLE studies are provided below by the ERG for completeness.

3.3.1 Clinical evidence from the ATTRACT trial

3.3.1.1 Renal function in ATTRACT

The CS states that the pre-specified criteria for comparability of migalastat and ERT in the ATTRACT trial were met for both the co-primary $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$ outcomes (CS Table C9.14). However, this does not apply to the [redacted] analysis of $eGFR_{CKD\text{-}EPI}$ since the difference in this GFR outcome between the migalastat and ERT groups [redacted] the pre-specified 2.2 mL/min/1.73m^2 (Table 12~~Table 12~~). Mean and median changes in the co-primary GFR outcomes are presented in the CS as graphs and are reproduced below (Figure 6~~Figure 6~~).The direction of the difference in mean changes between trial arms [redacted]; however, [redacted] indicate that there is [redacted] for these outcomes. For instance, the 95% confidence interval for the annualised mean change in $mGFR_{iohexol,}$ in the ERT group ITT analysis shown in Table 12~~Table 12~~ [redacted].

Point estimates for the secondary GFR outcome in the ATTRACT trial, change in $eGFR_{MDRD}$, were [redacted] in the migalastat and ERT arms. However, as with the co-primary outcomes the [redacted] (Table 12~~Table 12~~).

The CS does not comment on the clinical implications of the different GFR measures. Based on clinical expert advice and studies in the literature,[33] the ERG regards the measured GFR as more reliable then the estimated GFR outcomes. However, this does not particularly influence interpretation given [redacted].

Table 12 Renal function in the ATTRACT trial based on (a) ITT and (b) modified ITT populations

	Migalastat **(a) N=36, (b) N=34**	**ERT** **(a) N=24, (b) N=18**	**Difference**
$mGFR_{iohexol,}$ LS mean (95% CI) annualised change, 0-18	(a) [redacted] (b) −4.35 (−7.65, −1.06)	(a) [redacted] (b) −3.24 (−7.81, 1.33)	(a) −[redacted][a] (b) −1.11

months, mL/min/1.73m^2			
$eGFR_{CKD-EPI,}$ LS mean (95% CI) annualised change, 0-18 months, mL/min/1.73m^2	(a) [redacted] (b) −0.40 (−2.27, 1.48)	(a) [redacted] (b) −1.03 (−3.64, 1.58)	(a) [redacted][a] (b) 0.63
$eGFR_{MDRD,}$ LS mean (95% CI) annualised change, 0-18 months, mL/min/1.73m^2	(a) not reported (b) [redacted]	(a) not reported (b) [redacted]	(b) [redacted][a]
24-hour urine protein, mean (95% CI) change, 0-18 months, mg/day	(a) not reported (b) [redacted]	(a) not reported (b) [redacted]	(b) [redacted][a]
24-hour urine albumin: creatinine ratio, mean (95% CI) change, 0-18 months, mg/nmol	(a) not reported (b) [redacted]	(a) not reported (b) [redacted]	(b) [redacted][a]

LS: least squares
[a] calculated by ERG
[b] also reported as -4.23 by the CS (Table C9.14)

As shown in Table 12~~Table 12~~, the 24-hour urinary protein concentration and the albumin: creatinine ratio in the ATTRACT trial [redacted] in both the migalastat and ERT groups relative to baseline, but the [redacted] were [redacted] in the migalastat group. For both treatment groups, [redacted].

Bars show 95% CI for means and inter-quartile ranges for medians

Figure 6 Mean and median annualised changes in the co-primary outcomes of ATTRACT analysed in the modified ITT population

3.3.1.2 Cardiac function in ATTRACT

The CS presents the change in left ventricular ejection fraction (LVEF) over 18 months in the ATTRACT trial, (CS Table C9.13) and states that [redacted] (CS page 107). As shown below (CS data reproduced in Table 13~~Table 13~~) there was a slight decrease in LVEF in the migalastat arm and slight increase in the ERT arm, but the changes from baseline and difference between the groups were less than 2% and the confidence intervals for both groups include zero.

The CS (page 106) reports that the left ventricular mass index (LVMI) showed a [redacted] (CS data are reproduced in Table 13~~Table 13~~) and states that in the ERT group the value at 18 months was not significantly different from

baseline. This is supported by graphs in the CS which are reproduced in Figure 7~~Figure 7~~ below. However, the numbers of patients indicated in Figure 7~~Figure 7~~ are lower than those specified in the modified ITT population and differ between the 6-monthly sampling times. Reasons for these missing data are not explained in the CS (except that one patient at baseline in the migalastat group had missing echocardiogram data; footnote in CS Table C9.15).

Table 13 Cardiac outcomes in the ATTRACT trial based on the modified ITT population

	Migalastat (N=34)	ERT (N=18)	Difference[a]
LVEF, median change [b] (95% CI), 0-18 months, %	[redacted]	[redacted]	[redacted]
LVMI, mean change (95% CI), 0-18 months, g/m^2	−6.6 (−11, −2.2)[c]	−2 (−11, 7)[c]	−4.6

[a] calculated by ERG
[b] CS reports median with 95% CI – company clarified that this should be the mean
[c] decimal places are as reported in the CS

The CS provides a breakdown of the change in LVMI in the migalastat group according to patients' sex and whether they had left ventricular hypertrophy (LVH) at baseline (CS Table C9.15). These data suggest that [redacted]. A comparable breakdown of LVMI change by sex and LVH status is not provided for the ERT group.

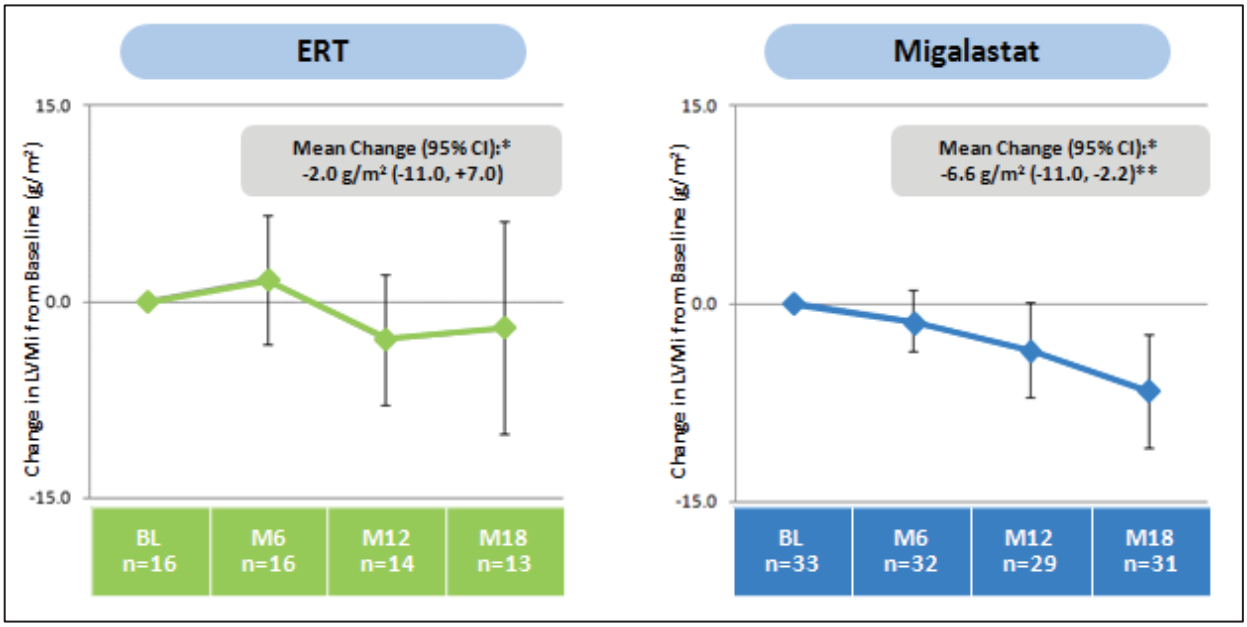

Figure 7 Left ventricular mass index change in the ATTRACT trial

Results for the pre-specified outcomes of left ventricular posterior wall thickness (LVPWT), intra-ventricular septal wall thickness (IVSWT), and functional diastolic and systolic grade are not presented, except for a statement that [redacted] (CS page 107).

3.3.1.3 Composite outcome in ATTRACT

The CS briefly mentions the results of the composite clinical outcome in the ATTRACT trial (CS Table C19.6), reproduced below in Table 14~~Table 14~~. During the 18-month treatment period, the proportion of patients who had a renal, cardiac, or cerebrovascular event or died was 29% (10/34) of patients who switched from ERT to migalastat compared to 44% (8/18) of patients who remained on ERT. Overall, renal events were the most common, followed by cardiac events. No deaths occurred.

Table 14 Composite outcome in the ATTRACT trial based on the modified ITT population

	Migalastat (N=34)	**ERT (N=18)**	**Difference[a]**
Any event up to 18 months, % (n/N) of patients	29 (10/34) (95% CI 14.1, 44,7)	44 (8/18) (95% CI 21.5, 67.4)	−15
Renal events up to 18 months, % (n/N) of patients	24 (8/34) Increased proteinuria 6 Decreased GFR 2	33 (6/18) [b] Increased proteinuria 4 Decreased GFR 3	−9
Cardiac events up to 18 months, % of patients	6 (2/34) Chest pain 1 VT/Chest pain 1	17 (3/18) Cardiac failure 1 Dyspnoea 1 Arrhythmia 1	−11
Cerebrovascular events up to 18 months, % (n/N) of patients	0	6 (1/18) TIA 1	−6
Death up to 18 months, % of patients	0	0	0

TIA: transient ischaemic attack; VT: ventricular tachycardia
[a] calculated by ERG
[b] CS states number of patients with events was n=6 but events are reported for n=7

3.3.1.4 Biochemical outcomes in ATTRACT

The CS states that in patients with an amenable mutation, lyso-Gb3 levels remained low and stable throughout the 18-month treatment period in both treatment groups. Data from the CS (Table C9.13) are reproduced in Table 15~~Table 15~~.

The CS presents graphs showing changes in plasma lyso-Gb3 in the subgroups of patients with and without amenable mutations (CS Figure C9.10). Migalastat had the same effect as ERT in maintaining low levels of lyso-Gb3 in patients with amenable mutations, whilst in patients without amenable mutations lyso-Gb3 increased in the migalastat group but not the ERT group. The CS states that these findings support the validity of the Migalastat Amenability Assay in identifying amenable mutations. However, the subgroup without amenable mutations has a very small sample size (2 patients in each group); these subgroup data are not reproduced here.

For the outcome of α-Gal A activity in peripheral blood mononuclear cells the CS (page 109) states that normal α-Gal A activity is approximately 22 nmol/h/mg (Germain et al., draft Manuscript).[21] The CS reports that,

[redacted]. The CS does not report baseline α-Gal A activity for females or for the total population. By 18 months,

[redacted] (Table 15~~Table 15~~).

Table 15 Biochemical outcomes in the ATTRACT trial based on the modified ITT population

	Migalastat (N=34)	ERT[a] (N=18)	Difference[b]
Plasma lyso-Gb3, mean (95% CI) change, 0-18 months, nmol/L	[redacted]	[redacted]	[redacted]
α-gal A activity in PMBC, mean (95% CI) change, 0-18 months, nmol/h/mg	[redacted]	[redacted]	[redacted]
α-Gal A activity in PMBC, median change, 0-18 months, nmol/h/mg	[redacted]	[redacted]	[redacted]

α-gal A: alpha-galactosidase A; PMBC: peripheral mononuclear blood cells
[a] Table C9.13 in the CS refers to a placebo group instead of ERT group – this is assumed to be a typographic error
[b] calculated by ERG

3.3.1.5 Health related quality of life in ATTRACT

The ATTRACT trial HRQoL outcomes (CS Tables C9.13 and C9.17) are reproduced in Table 16~~Table 16~~. The CS does not provide clinical interpretation of these results, but states that SF-36 scores (0-100 scale) were [redacted] in these scores over the 18-month study period. The CS mentions that scores on the BPI Pain Severity Component (where 10=maximum pain) indicate that [redacted].

Table 16 HRQoL scores in the ATTRACT trial based on patients without missing data

	Migalastat	ERT[a]	Difference[b]
SF-36 PCS score, mean (95% CI) change, 0-18 months	[redacted] (n=31)	[redacted] (n=16)	[redacted]
SF-36 MCS score, mean (95% CI) change, 0-18 months	[redacted] (n=31)	[redacted] (n=17)	[redacted]
BPI short form composite score, mean (95% CI) change, 0-18 months	[redacted] (n=34)	[redacted] (n=17)	[redacted]

BPI: Brief Pain Inventory; MCS: Mental Component Summary; PCS: Physical Component Summary
[a] Table C9.13 in the CS refers to a placebo group instead of ERT group – this is assumed to be a typographic error
[b] calculated by ERG

The CS does not explain how missing HRQoL data were handled, and it appears that only patients who had complete HRQoL records were analysed. As can be seen in Table 16~~Table 16~~, the number of missing HRQoL data (compared to the sample size that would be expected for the mITT population, i.e. n=34 for migalastat and n=18 for ERT) varied with the outcome. The proportion of missing data ranged from 0% (0/34 for the BPI short form results in the migalastat group) to 9% (3/34 for both SF-36 outcomes in the migalastat group), and 11% (2/18 for the SF-36 PCS results in the ERT group).

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3.3.2 Clinical evidence from the FACETS trial

3.3.2.1 Renal function in FACETS

For the FACETS trial, the CS acknowledges that the 6-month trial duration would generally be considered too short to reliably show changes in GFR. The changes in the measured and estimated GFR outcomes from 0-6 months were all less than 3.0 mL/min/1.73m^2 for both the migalastat and placebo groups (Table 17~~Table 17~~). The CS presents standard errors rather than 95% CIs. Multiplying the standard errors by 1.96 to obtain approximate 95% CIs would give confidence intervals for all three GFR outcomes that would span the spectrum of possible positive, zero, or negative changes from baseline, for both the migalastat and placebo groups, indicating wide uncertainty in these outcomes.

Table 17 Renal function in the FACETS trial based on the ITT population

	Migalastat (n=34)	Placebo (n=33)	Difference[a]
$mGFR_{iohexol,}$ mean ± SE change, 0-6 months, mL/min/1.73m^2	−1.19 ± 3.4	0.41 ± 2.0	−0.78
$eGFR_{CKD-EPI,}$ mean ± SE change, 0-6 months, mL/min/1.73m^2	1.80 ± 1.5	−0.3 ± 1.4	2.10
$eGFR_{MDRD,}$ mean ± SE change, 0-6 months, mL/min/1.73m^2	[redacted]	[redacted]	[redacted]
Urine protein, LS mean change, 0-6 months, mg/day	[redacted]	Not reported	[redacted]
Urine albumin, LS mean change, 0-6 months, mg/day	[redacted]	Not reported	[redacted]
Urine creatinine, LS mean change, 0-6 months, mg/day	Not reported	Not reported	[redacted]

[a] calculated by ERG

As noted above (Table 8~~Table 8~~), the CS defined 24-hour protein, urine and creatinine as secondary outcomes in FACETS, but incomplete results are reported for protein and albumin (Table 17~~Table 17~~) and only narrative results are given for creatinine [redacted]. The CS mentions narratively that there was [redacted] between the migalastat and placebo groups in the changes from baseline [redacted], but there was [redacted].

In addition to reporting renal function in the FACETS trial, the CS also reports a comparison of the annualised change in $eGFR_{MDRD}$ in patients receiving migalastat in FACETS against that of an international reference untreated population with Fabry disease (CS Page 115). The ERG is unclear why the company used the estimated rather than measured GFR for this comparison and unclear why longer-term measured GFR from the ATTRACT trial was not used in preference to the short-term FACETS results. As this comparison does not inform the current appraisal it is not discussed further here.

3.3.2.2 Cardiac function in FACETS

No quantitative data for cardiac outcomes in the 6-month FACETS trial are reported in the CS. The CS states that, as would be expected after a short time, no changes in LVMI were seen (CS page 116).

3.3.2.3 Biochemical outcomes in FACETS

Changes in interstitial capillary GL3 inclusions were analysed in the ITT population, and changes in urinary GL3 and in plasma lyso-Gb3 were analysed in the amenable mutations population (CS Table C9.19). In addition, the company conducted a post-hoc analysis in the amenable mutations population for one of the interstitial cell GL3 inclusions secondary outcomes. Results of these analyses are reproduced in Table 18~~Table 18~~.

The results show that there was a reduction in interstitial capillary GL3 inclusions over 6 months which was larger in the migalastat group than the placebo group. This is supported by the primary outcome of the change in the proportion of patients who had a ≥50% reduction in GL3 inclusions, as well as the secondary and tertiary outcomes relating to the changes in numbers of GL3 inclusions in interstitial capillaries (Table 18~~Table 18~~). However, only the post-hoc analysis results (amenable mutations population) and tertiary outcome analysis results (ITT population) were statistically significant.

Urinary GL3 concentrations declined in both study groups, but to a greater degree in the migalastat group than the placebo group (Table 18~~Table 18~~). The CS states (page 117) that overall there was high variability in urine GL3 values, but does not discuss the clinical interpretation of these findings.

Plasma lyso-Gb3 concentrations during the FACETS trial declined in the migalastat group but not the placebo group, and this difference between groups after 6 months was statistically significant (Table 18~~Table 18~~).

Table 18 Biochemical outcomes in the FACETS trial

	Migalastat	Placebo	Difference
≥50% reduction in IC GL3 inclusions,0-6 months, mean (95% CI) % of patients (ITT population) (primary outcome)	40.6	28.1	12.5 (−13.4, 37.3) (p=0.30)
Number of GL3 inclusions per IC, mean (95% CI) change, 0-6 months (ITT population with amenable mutations) (post-hoc analysis[a])	−0.25	0.07	−0.3 (−0.6, −0.1) (p=0.008)
Number of GL3 inclusions per IC, median % change, 0-6 months (ITT population) (secondary outcome)	−40.8	−5.6	35.2 (p=0.097)
% of IC with zero GL3 inclusions, LS mean change, 0-6 months (ITT population) (tertiary outcome)	7.3	1.3	6.0 (0.2, 11.7) (p=0.042)
Urinary GL3, mean ± SE change, 0-6 months, ng/mg creatinine (ITT population with amenable mutations)	−361 ± 169	−147 ± 217	−214[b]
Plasma lyso-Gb3, mean ± SE (95% CI) change, 0-6 months, nmol/L (ITT population with amenable mutations)	−11.2 ± 4.8	0.58 ± 2.4	−11.4 (−18.7, −4.1) (p=0.003)

IC: interstitial capillary; LS: least squares
[a] post-hoc analysis (secondary outcome) based on the ITT population with amenable mutations
[b] calculated by ERG

3.3.2.4 Health related quality of life in FACETS

The FACETS trial HRQoL outcomes for the period from baseline to 6 months (CS Table C9.19) are reproduced in Table 19~~Table 19~~ for the GSRS. The CS states that the GSRS evaluates the level of discomfort due to 15 gastrointestinal symptoms. However, results for only five domains are presented. The CS mentions (page 132) that the minimal clinically important difference (MCID) for the diarrhoea domain in the GSRS is an improvement from baseline ≥0.4 units, based on Chan and colleagues (2006).[41] The CS states that, while calculated in a non-Fabry population,[41] it is likely that this MCID also represents a clinically relevant improvement in the Fabry population. Based on this estimate of the MCID, 69% of the migalastat-treated patients experienced a clinically relevant change versus 11% of the placebo-treated patients (p=0.012). As shown in Table 19~~Table 19~~, GSRS scores indicated a greater improvement in diarrhoea and

reflux symptoms in the migalastat group compared to the ERT group, but no difference between the groups for indigestion, constipation or abdominal pain.

Results for the SF-36 (CS Table C9.19) and BPI Severity Component Scores (CS page 118) are presented only narratively. The CS states that for the SF-36 Physical Component Score differences between groups or changes from baseline were not found at 6 months. Results for the SF-36 Mental Component Summary are not reported. For the BPI Severity Component Scores, the CS states that from baseline to month 6, no differences between migalastat and placebo groups were observed.

Table 19 GSRS scores in the FACETS trial

LS mean change, 0-6 months [a]	**Migalastat**	**Placebo**	**Difference[b]**
Diarrhoea	−0.3	0.2	−0.5 (p<0.05)
Reflux	0	0.2	−0.2
Reflux for subjects symptomatic at baseline (post-hoc analysis)	−0.5	0.3	−0.8 (p≤0.05)
Indigestion	−0.1	−0.1	0
Constipation	0.1	0.2	−0.1
Abdominal pain	0	0	0

LS: least squares; GSRS: Gastrointestinal Symptoms Rating Scale
[a] p-values are reported in the CS for selected GSRS domains for the amenable mutations population (not extracted here)
[b] difference calculated by ERG; p-values reported in CS

Key limitations of these HRQoL results are that the CS does not report sample sizes for the HRQoL outcomes and so the number of missing data is unclear; selective results are presented; and no adjustment was made for conducting multiple statistical tests.

3.3.3 Clinical evidence from OLE studies

3.3.3.1 Renal function in OLE studies

ATTRACT trial patients

The CS reports 30-month data from the OLE period following the ATTRACT trial (i.e., 18 months of randomised treatment plus 12 months of open-label migalastat treatment). The CS states that the 30-month analyses include only patients with amenable mutations and baseline/post-baseline measures of estimated and measured GFR. It is unclear in the CS whether the OLE data are for patients only from the migalastat arm of ATTRACT or also those

who received ERT before entering the OLE. A poster by Bichet and colleagues[32] mentions that 49 patients received ≥1 dose of migalastat during the combined 30 months, which is larger than the number randomised to migalastat, suggesting the OLE data are not only for patients from the migalastat arm. The 30-month mean annualised rate of change from baseline in $mGFR_{iohexol}$ was −2.8 mL/min/1.73 m^2 (95% CI −4.8, −0.7; n=30) and the change in $eGFR_{CKD-EPI}$ was −1.7 mL/min/1.73 m^2 (95% CI −2.7, −0.8; n=31), both indicating a decline (sample sizes are from Bichet and colleagues[32]).

FACETS trial patients

The CS reports renal function for patients who received migalastat up to 24 months from the baseline of the FACETS trial (Table 20~~Table 20~~). For the GFR outcomes the CS does not identify which of the patients in the OLE had previously received migalastat or placebo, so the results are for a combination of patients who had received migalastat for either 18 or 24 months in total. The annualised changes in mGFR showed a decline and the eGFR results were inconsistent, although the confidence intervals include zero in all cases (Table 20~~Table 20~~). The 24-hour urinary protein in the OLE [redacted] over 24 months in patients who received 24 months of migalastat, and [redacted] over 18 months in patients who received 18 months of migalastat.

Table 20 Renal function in the FACETS OLE study

Change, 0-18/24 months	**Migalastat**
$mGFR_{iohexol,}$ mean (95% CI) [median] change, mL/min/1.73m^2	−1.51 (−4.20, 1.18) [−1.03] (n=37)
$eGFR_{CKD-EPI,}$ mean (95% CI) [median] change, mL/min/1.73m^2	−0.30 (−1.65, 1.04) [0.25] (n=41)
$eGFR_{MDRD,}$ mean (95% CI) [median] change, mL/min/1.73m^2	[redacted] (n=41)

In addition to the 24-month follow up data, the CS also reports limited renal function results for an average (not stated whether mean or median) of 36 months (range 18-54 months) in the OLE period. However, this is reported only for the estimated GFR ($eGFR_{CKD-EPI}$) rather than measured GFR. Mean change 0-36 months was [redacted] mL/min/1.73m^2 [redacted]. The CS states that this compares favourably with long-term GFR decline experienced by untreated patients with Fabry disease (−2.2 to −12.2 mL/min/1.73m^2) and is within the range of decline

seen in healthy adults with ageing (−1 mL/min/1.73m^2) (references cited; CS page 119). The ERG is concerned about the small sample sizes for these long term OLE results. According to a source cited in the CS (EMA Summary of clinical effectiveness[42]), at 36 months the numbers of patients in the OLE were n=14 from the migalastat arm and n=11 from the placebo arm, but by month 54 the respective numbers were n=0 and n=1 (Table 26 in the reference[42]). Given that the results are quoted for an average of 36 months, there is a lack of clarity around how many patients contributed data at which times and what the proportions of patients from the migalastat and placebo arms of FACETS were.

3.3.3.2 Cardiac function in OLE studies

ATTRACT trial patients

The CS presents 30-month data from ATTRACT plus the OLE (18 months randomised treatment plus 12 months open-label migalastat treatment), for patients with amenable mutations and baseline/post-baseline measures of LVMI. The mean annualised change from baseline in LVMI (n=31) was −3.8 g/m^2 (95% CI −8.9, 1.3). In patients with LVH at baseline (n=11), the reduction to month 30 for migalastat was statistically significant based on the 95% CIs (-10.0 [95% CI: -16.6, -3.3]).

FACETS trial patients

The CS presents LVMI changes up to 18 months (for patients on migalstat following placebo) and 24 months (for patients continuing on migalastat) combined (CS Table C9.22). The CS states that in patients with amenable mutations, LVMI was significantly reduced after 18/24 months of migalastat treatment ($p<0.05$) (baseline n=44, 18/24 months n=27). The change was −7.69 g/m^2 (95% CI −15.4, −0.0009).

The CS provides only a brief narrative summary of other cardiac changes up to 18/24 months after the FACETS trial (CS page 116). IVSWT decreased by 5.2%; LVPWT remained stable; LVEF and fractional shortening were generally normal at baseline and remained stable; and systolic and diastolic function grades were [redacted].

Further limited data are provided in the CS for patients with amenable mutations who received a total of 30 or 36 months of migalastat in the FACETS trial plus OLE study (CS Table C9.26). The mean LVMI change from baseline to 30/36 months (n=[redacted]) was [redacted] g/m^2 ([redacted]).

These long-term data are subject to the same concerns about small sample sizes as mentioned above for renal function (section 3.3.3.1~~3.3.3.1~~).

3.3.3.3 Biochemical outcomes in OLE studies

ATTRACT trial patients

The CS does not report any biochemical outcomes for patients in the OLE studies who were from the ATTRACT trial.

FACETS trial patients

The CS briefly mentions biochemical outcomes for the amenable mutations population in the OLE following FACETS. The activity of α-gal A in peripheral blood mononuclear cells [redacted] in males (CS pages 117-118). For plasma lyso-Gb3 the CS states (page 116) that the reduction which occurred in the migalastat group during the 6-month randomised period of FACETS remained stable at 12 months, whilst patients who had previously received placebo and switched to migalastat showed a reduction in plasma lyso-Gb3 at 12 months. The CS does not specify the sample sizes for these outcomes.

3.3.3.4 HRQoL outcomes in OLE studies

ATTRACT trial patients

The CS does not report any HRQoL outcomes for patients in the OLE studies who were from the ATTRACT trial.

FACETS trial patients

The CS reports changes in scores for five of the 15 GSRS domains (CS Table C9.25) and these are reproduced in Table 21~~Table 21~~. After 18 or 24 months of migalastat treatment patients had significant improvement (i.e. confidence intervals excluded zero) in the diarrhoea and indigestion domains. The CS states that there was a trend for improvement in the reflux and constipation domains whilst symptoms of abdominal pain remained stable.

Table 21 GSRS scores in the FACETS OLE study

GSRS domain	Change from baseline after 18/24 months of migalastat, mean (95% CI)
Diarrhoea domain	−0.5 (−0.9, −0.1)
Reflux domain	−0.2 (−0.5, 0.2)
Indigestion domain	−0.4 (−0.7, −0.04)
Constipation domain	−0.4 (−0.7, 0.0)
Abdominal pain domain	−0.2 (−0.5, 0.1)

For the SF-36, the CS only reports changes in scores up to 18 or 24 months for the Vitality and General Health domains (CS Table C9.24). These were 4.0 (95% CI 0.1, 8.0) and 4.5 (95% CI 0.2, 8.9) respectively. The other SF-36 domains were stated to have remained stable.

For the BPI Severity Component Scores the CS states (page 118) that scores did not differ from baseline to month 6 or from month 6 to month 24.

When interpreting the HRQoL scores the ERG urges caution since not all of the HRQoL domains have been reported. Furthermore, the analyses were based on the amenable mutations population of patients who provided sufficient data, but the sample sizes for the different HRQoL outcomes are not reported. Moreover, the OLE results combine patients from both arms of FACETS.

3.3.4 Sub-group analyses

The CS states when referring to the decision problem (CS page 21) that no subgroups were specified, but states later that subgroup analyses were conducted in the ATTRACT and FACETS trials (CS page 95). Analyses in the ATTRACT trial were carried out according to sex and proteinuria. The CS does not report results of these subgroup analyses, except for mentioning the LVMI cardiac outcome separately for males (but not separately for females). The CS reports results of the lyso-Gb3 outcome in ATTRACT separately by subgroups with and without amenable mutations, which was not mentioned as a pre-specified subgroup analysis.

The CS states that in FACETS exploratory analysis of the primary endpoint were conducted for a range of different subgroups and combinations (see above, section 3.1.3.1~~3.1.3.1~~).These are not reported in the CS.

3.3.5 Mixed treatment comparison

As described above (section 3.1.73.1.7), the company did not conduct a mixed treatment comparison.

3.3.6 Adverse events

Data on adverse events are provided by the company from the ATTRACT trial (Table 22Table 22), the FACETS trial (Table 23Table 23) and also the OLE studies following the FACETS trial (Table 24Table 24). The CS also briefly gives a narrative summary (CS section 9.7.3) of migalastat safety across the company's development programme for migalastat. This does not identify any additional safety issues beyond those reported for the ATTRACT and FACETS trials.

Discontinuations due to adverse events

The CS reports that there were no discontinuations due to treatment emergent adverse events (TEAE) in either the ATTRACT or FACETS trials. Two patients in FACETS discontinued due to (unspecified) serious adverse events (SAE) which were deemed unrelated to migalastat therapy. In the OLE study two patients from ATTRACT discontinued as a result of adverse events that were judged possibly related to migalastat therapy. These were mild proteinuria (classed as a SAE) in a patient who had previously received migalastat and was found to be pregnant; and mild diarrhoea and mild vomiting (classed as TEAE) in a patient who had previously received ERT. The CS (Figure C9.6) implies that [redacted] of the migalastat group patients and [redacted] of the placebo group patients in the FACETS trial who entered the OLE study subsequently discontinued, but the CS does not state that any discontinuations in the OLE to FACETS were due to adverse events.

Table 22 Adverse events in the ATTRACT trial

	Migalastat (n=36)	ERT (n=21)
Proportion with TEAE, %	[redacted]	[redacted]
Discontinuation due to TEAE, %	0	0
Most frequent TEAE (≥10%), n (%)		
Nasopharyngitis	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Procedural pain	[redacted]	[redacted]
SAE	[redacted]	[redacted]

SAE: serious adverse event; TEAE: treatment emergent adverse event

Frequencies of adverse events

No deaths occurred in either of the trials or the OLE studies. In the ATTRACT trial (Table 22~~Table 22~~) the majority of patients in both the migalastat and ERT arms (94-95%) experienced TEAE, most frequently nasopharyngitis and headache (affecting 24-33% of patients). SAE in ATTRACT were less frequent in the migalastat arm than the ERT arm (19% versus 33%) and

were all judged to be unrelated to migalastat therapy; however, the CS does not list the specific SAE which occurred.

In the FACETS trial (Table 23~~Table 23~~) the majority of patients (91%) in both the migalastat and placebo arms experienced TEAE. The most frequent TEAE were headache and nasopharyngitis, and these were both more frequent in the migalastat arm (35% and 18% respectively) than in the placebo arm (21% and 6%).

Table 23 Adverse events in the FACETS trial

	Migalastat (n=34)	**Placebo (n=33)**
Patients with any TEAE, %	[redacted]	[redacted]
Discontinuation due to TEAE, %	0	Not reported
Patients with any SAE, n	[redacted]	[redacted]
TEAE ≥10%, n (%)		
Headache	12 (35)	7 (21)
Nasopharyngitis	6 (18)	2 (6)
Fatigue	4 (12)	4 (12)
Paraesthesia	4 (12)	4 (12)
Nausea	4 (12)	2 (6)
Pyrexia	4 (12)	[redacted]
Pain in extremity	[redacted]	4 (12)

[a] The FACETS draft manuscript [21] differs from the CS in stating that [redacted] patients had serious adverse events: [redacted] in the migalastat arm and [redacted] in the placebo arm

Adverse events in OLE studies

The CS does not mention any adverse events in the OLE study following the ATTRACT trial, apart from those which led to discontinuation for two patients (described above).

When reporting adverse events among patients in the OLE studies who were previously in the FACETS trial, the CS does not distinguish between patients who previously received migalastat and those who previously received placebo (Table 24~~Table 24~~). The most frequent adverse events in the OLE period were headache and procedural pain (11-14%) during months 7-12, and proteinuria, headache and bronchitis (11-16%) during months 13-24.

Table 24 Adverse events in the FACETS + OLE studies

7-12 months open-label extension (referred to in CS as 'stage 2')	
Patients with any SAE, n	[redacted]
TEAE ≥10%, n (%)	
Headache	9 (14)
Procedural pain	7 (11)
Nasopharyngitis	5 (8)
Arthralgia	[redacted]
Tachycardia	3 (5)
13-24 months open-label extension (referred to in CS as 'stage 3')	
Patients with any SAE, n	[redacted]
TEAE ≥10%, n (%)	
Proteinuria	9 (16)
Headache	6 (11)
Bronchitis	6 (11)

SAE: serious adverse event; TEAE: treatment emergent adverse event

The CS states that analyses of vital signs, physical findings, laboratory, and ECG parameters did not reveal any clinically relevant effect of migalastat in either the FACETS or ATTRACT trials.

Overall, the adverse events data submitted by the company do not raise any safety concerns over the use of migalastat.

3.4 Summary of clinical evidence submitted by the company

The studies providing clinical effectiveness evidence for migalastat are limited. Of the two pivotal RCTs reported in the CS, only the ATTRACT trial is directly relevant to the NICE scope.

The ERG has some concerns about the quality and reporting of the ATTRACT and FACETS RCTs. Despite randomised group allocation, there were baseline imbalances in patient characteristics between the trial arms in both RCTs, which is of particular concern in RCTs with small participant numbers. In the ATTRACT trial these related to mean age (4 years older in the migalastat group), mean time since diagnosis (3.2 years shorter in the migalastat arm), and mean 24-hour urine protein (93 mg less in the migalastat arm). Although ITT analyses were

undertaken based on all randomised patients in both trials, the ITT population included some patients who were found after randomisation not to have amenable mutations and therefore the CS emphasises the results of 'modified ITT' analyses (mITT) which excluded these patients. In the ATTRACT RCT, the mITT population excluded patients with other protocol violations as well as non-amenable mutations and was effectively a per protocol population. The term 'modified ITT' is therefore potentially misleading (and has different meaning in the two RCTs). Although some longer-term data are available from the OLE studies for several outcomes, these do not distinguish how many patients in the OLE were from the migalastat or the comparator arm in each trial.

Clinical effectiveness evidence from the ATTRACT trial

In the ATTRACT RCT, the company's ad hoc criteria for demonstrating 'comparability' of migalastat and ERT were met for the primary mGFR outcome analysed according to the ITT and mITT populations, but confidence intervals indicated wide uncertainty. Results for eGFR were also reported but were inconsistent between two methods of estimation. Data for patients who continued on migalastat in the OLE period showed that the mGFR declined over a 30-month period. However, due to the wide confidence intervals for mGFR in the ATTRACT trial it is difficult to determine whether the change in mGFR in the OLE period represents improvement, stabilisation, or worsening of renal function. Furthermore, it was not reported how many patients in the OLE were from the migalastat and ERT arms of the ATTRACT trial. The 24-hour urine protein and albumin:creatinine ratio both increased during ATTRACT but to a smaller extent in the migalastat group than the ERT group. The changes are uncertain, however, as confidence intervals for both outcomes included zero change.

The ATTRACT trial only reported cardiac outcomes for mITT analyses, and these suggest that migalastat did not detectably influence LVEF but did improve left ventricular mass during the 18-month trial period.

Changes in biochemical outcomes reported in ATTRACT showed no clear pattern, except that activity of the target enzyme α-galactosidase A in white blood cells increased in the migalastat group but not the ERT group. This change reflects the mode of action of migalastat but the outcome is not used consistently in clinical decision making.

HRQoL was assessed using the SF-36 and the BPI. The analysis population for HRQoL was smaller than the mITT population, as only mITT population patients who had complete HRQoL records were analysed. Mean scores for the SF-36 Physical Component Summary, SF-36 Mental Component Summary and the BPI increased marginally in the migalastat group over 18 months and slightly decreased in the ERT group; however, the differences were small and the confidence intervals in all cases included zero.

The only outcomes from the ATTRACT trial used directly in the company's economic analysis were adverse events (see section 4 below), although renal function outcomes were cited in support of the company's assumption of clinical equivalence of migalastat and ERT. Given the uncertainty in the results of the primary outcomes and the methodological limitations of the ATTRACT RCT noted above, the ERG does not agree that the ATTRACT trial provides an unbiased estimate of the clinical equivalence of migalastat and ERT.

Clinical effectiveness evidence from the FACETS trial

The primary outcome in the FACETS trial, the six-month change from baseline in the proportion of patients who had a ≥50% reduction in interstitial capillary GL3 inclusions, analysed in the ITT population, was higher in the migalastat arm than the placebo arm but the difference between groups was not statistically significant.

The six-month change in mean (±SE) mGFR in the ITT analysis in FACETS showed a decline in renal function in the migalastat group and a slight increase in the placebo group, but standard errors suggest no significant difference from zero change. The CS also reports the mean change in mGFR for FACETS patients who continued on migalastat for a further 18 months in the OLE period, but it does not distinguish between those who received a total of 18 months of migalastat (6 months of placebo in FACETS + 18 months of migalastat in the OLE) and those who received a total of 24 months of migalastat (6 months of migalastat in FACETS + 18 months of migalastat in the OLE). The mean change in GFR from 0-24 months for these two groups combined showed a decline but with 95% confidence intervals including zero change. The FACETS trial also reported two different measures of eGFR but these showed inconsistent changes from baseline.

FACETS did not report quantitative results for both the trial arms for any other renal outcomes, for any cardiac outcomes, or for HRQoL assessed using the SF-36 or BPI. Quantitative HRQoL

results were reported for the Gastrointestinal Symptoms Rating Scale (GSRS), but only for five of 15 possible symptom domains. Changes in GSRS scores suggested a greater improvement in diarrhoea and reflux symptoms in the migalastat group compared to the ERT group, but no difference between the groups for indigestion, constipation or abdominal pain. However, sample sizes were not reported. Due to the short duration of the trial it is inadvisable to attempt to draw any firm conclusions about effects of migalastat on HRQoL from these data.

Key limitations of the FACETS RCT are that it is not directly relevant to the scope and it had a relatively short duration (6 months), which is inadequate to clearly establish changes in renal, cardiac and HRQoL outcomes. As explained in section 4 below, no results from FACETS were used by the company to inform any of their analyses.

Adverse events

The most frequent adverse events in the ATTRACT RCT were nasopharyngitis and headache, and these did not differ in frequency between the migalastat and ERT groups. No deaths occurred in either the ATTRACT or FACETS RCTs or in the OLE studies. The CS states that no patients discontinued due to treatment-emergent adverse events in either RCT. Overall, the adverse events data submitted by the company do not raise any safety concerns over the use of migalastat. However, a potential limitation of the adverse events data is that the RCTs were of relatively short duration and the numbers of patients who completed the OLE studies were small ([redacted] patients from ATTRACT received a total of 30 months of migalastat therapy whilst 27 patients from FACETS received a total of 24 months of migalastat therapy).

4 ECONOMIC EVALUATION

4.1 Overview of the company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of treatments for Fabry disease.
ii) a report of an economic evaluation undertaken for the NICE HST process. The cost and health outcomes of migalastat are compared with ERT for patients with Fabry disease.
iii) A budget impact model of migalastat and ERT in England projecting expected costs over a 5-year period.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations of treatment for patients with Fabry disease. See section 3.1.13.1.1 of this report for the ERG critique of the search strategy.

The inclusion and exclusion criteria for the systematic review are listed in Appendix 17.1 of the CS (page 258). The inclusion criteria state that economic studies of treatment for patients with Fabry disease in adults would be included. The exclusion criteria state that studies with fewer than 10 patients would be excluded.

117 studies were identified from screening 538 titles and abstracts. Six studies were included for full review. Of these, three studies were cost analyses, budget impact studies or cost of illness studies, rather than cost effectiveness studies. The three cost effectiveness studies[1, 43, 44] evaluated ERT compared to no treatment. None of the studies considered treatment with migalastat.

The company applied the checklist suggested by NICE to the included references but did not provide a narrative of the results from the economic evaluations found. Differences in the structure of the three cost effectiveness studies are discussed in CS 12.1.3. The CS concludes on the basis of this review that a study by Rombach and colleagues[1] provided the best basis for the evaluation of migalastat.

The Rombach and colleagues[1] model is a Markov state-transition cost-effectiveness model comparing ERT to standard medical therapy (i.e. best supportive care) for a Dutch cohort of

patients with Fabry disease. The model consists of 11 health states: no symptoms; acroparesthesia (neuropathic pain in the extremities); symptoms (left ventricular hypertrophy, chronic kidney disease stage 1-4, or white matter lesions); ESRD; cardiac complications; stroke; ESRD + cardiac complications; cardiac complications + stroke; ESRD + stroke; ESRD + cardiac complications + stroke; death. Patients progress from the less severe to more severe health states. In addition patients may regress to the symptomatic stage from a more severe state after a kidney transplant. The model consists of 1-year cycles and follows a patient cohort from birth for 70 years. Transition probabilities and costs were estimated from the Dutch Fabry study.[1, 45]

4.3 Critique of the company's submitted economic evaluation

4.3.1 NICE reference case

The NICE reference case requirements were considered in the ERG's critical appraisal of the submitted economic evaluation as shown in Table 25~~Table 25~~.

Table 25 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	CS Table A1.1, page 20
Comparator: As listed in the scope developed by NICE	Partly	The company uses a blended comparator, 'ERT' which consists of a combination of agalsidase alfa and agalsidase beta
Perspective on costs: NHS and PSS	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Partly	The model includes the relevant health outcomes as health states. It is unclear how the clinical trial outcomes relate to long term outcomes in the model.
		continued

Table 25 - continued

NICE reference case requirements:	Included in submission	Comment
Type of economic evaluation: Cost consequence analysis with fully incremental analysis	Yes	Cost consequence model.
Synthesis of evidence on outcomes: Based on a systematic review	No	The company has assumed clinical equivalence
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Partly	Health effects measured in QALYs. The disutility for infusion did not use EQ-5D, but used a discrete choice experiment. All other utility values were measured by EQ-5D.
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Partly	The disutility for infusion did not use patients and / or carers, but used a sample of the general population. The utility values for the health states were reported directly from patients with Fabry disease.
Source of preference data: Representative sample of the UK population	Yes	The tariff used was from a UK population.
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% per annum for costs and health effects	Yes	

4.3.2 In general, the company model is in line with the NICE reference case. However, there are several aspects that deviate from the NICE reference case. Firstly, the company has used a blended comparator, rather than including all relevant ERT in

a fully incremental analysis. Secondly, the company has not based the outcomes of the model on a systematic review of the effectiveness of the treatments but instead assumed clinical equivalence. Thirdly, their estimate for the disutility of infusions was not measured using EQ-5D. Model Structure

The company's cost-consequence analysis uses a Markov model to estimate the costs and health effects of migalastat compared with ERT in people with Fabry disease. The analysis is conducted from an NHS and PSS perspective for the base case and a societal perspective is explored in sensitivity analysis. The cycle length is one year and the analysis consists of a lifetime horizon. A mid-cycle correction is applied to costs and health benefits. The starting population is based on the ATTRACT trial, with a start age of 48 years and starting states that replicate the pooled health states for migalastat and ERT from ATTRACT. Patients in the model do not have ESRD at baseline. The model assumes that 50% of the starting population is female, based on clinical opinion. Patients' progression through the model is based upon the progressive course of the disease, with the number of organ systems affected progressively increasing over time.

The model structure was informed by the company's systematic review of economic evaluations. The aforementioned Dutch model by Rombach and colleagues[1] was selected as most appropriate, but adapted slightly. The company stated the following criteria for selecting the model: appropriate Markov model structure with lifetime horizon and societal perspective; 11 disease states capturing symptoms of Fabry disease; and data for transition probabilities, utilities and costs were prospectively gathered from the Dutch Fabry cohort.[1, 45] The schematic for the Markov model is presented in Figure 8 (derived from CS Figure D12.1, page183).

The health states in the model represent the progression of Fabry disease over time. All health states are divided into incident (acute events) and prevalent (long term), whereby 'incident' refers to the first cycle and 'prevalent' refers to subsequent cycles in that health state. This structure allows patients experiencing an acute event to have different costs and consequences than patients who are in long term follow-up for that health state. Patients in the pain health state exhibit neuropathic pain and may progress to the CEFD health state or die. A patient who has progressed to CEFD has some or all of the following symptoms: white matter lesions, left ventricular hypertrophy and/or chronic kidney disease stages 1 through 4. From the CEFD health state, patients may progress to any single-complication state of ESRD, stroke, or cardiac complication. Patients have ESRD when they progress to chronic kidney disease stage 5.

Patients in the stroke health state have previously experienced a stroke. Cardiac complications patients may have one or more of the following complications: atrial fibrillation, rhythm disturbance requiring hospitalisation, pacemaker, cardiac congestion requiring hospitalisation, myocardial infarction, percutaneous coronary intervention, implantable cardiac defibrillator, or a coronary artery bypass graft. Patients in any single-complication health state (ESRD, stroke, cardiac complications) may remain in that state, progress to a state with a second complication, or die. Once patients experience a second complication, they can either progress to a third complication or die.

The model schematic contains two errors, as it implies that patients with ESRD + cardiac complications, and patients with cardiac complications + stroke, cannot progress to ESRD + cardiac complications + stroke; both transitions are allowed within the model. The model represents a simplified version of Fabry disease progression that does not allow patients with ESRD to have kidney transplants and does not capture different levels of chronic kidney disease, different severities of stroke, or different types of cardiac complications.

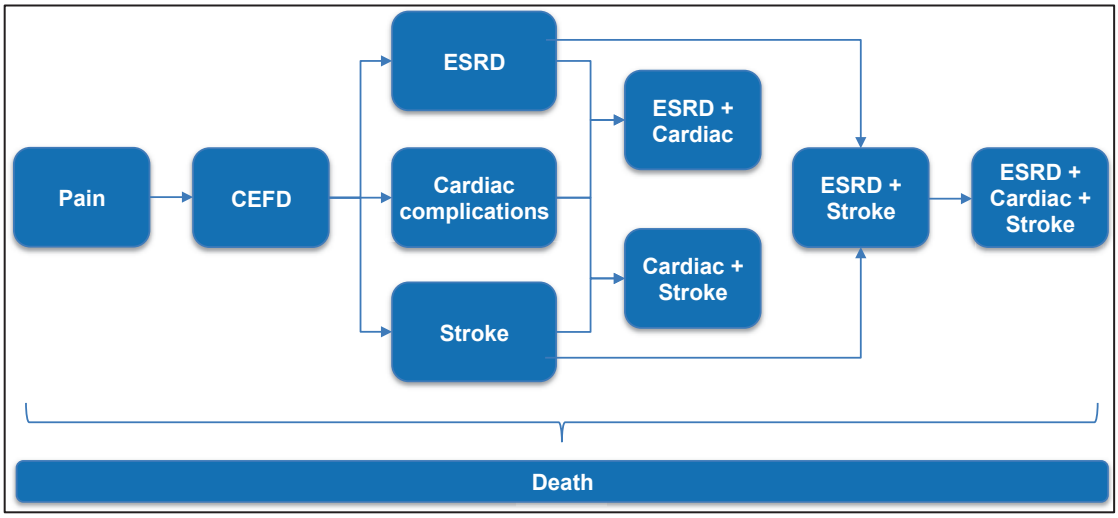

Figure 8 Company model schematic (CS Figure D12.1)

Although based on the model by Rombach and colleagues,[1] the company's model differs in the following ways:

- The Dutch model allows for disease regression due to kidney transplants, whilst the company model does not allow any health state improvement.

- The patients in the model by Rombach and colleages[1] start at birth and have transition probabilities calculated based on transitions from birth, whilst the company model begins at age 48 years.
- There is also some relabelling of health states; the acroparesthesia state from the Rombach and colleages[1] model is relabelled pain and the symptoms state is relabelled CEFD; these do not affect the transition probabilities.
- The asymptomatic health state is not included in the company's model, since it assumes diagnosis and initiation of treatment as a starting point.

The company lists the following structural assumptions in their model (as per CS Table 12.2, page 186):

- Migalastat has equivalent clinical effectiveness to both ERTs.
- Patients receiving migalastat continue treatment until death, whilst patients receiving ERT discontinue treatment.
- Data from the Dutch study (The Netherland registry for Fabry disease)[1, 45] are assumed representative of UK clinical practice.
- Treatment adherence is 100%.
- Transition probabilities do not vary over time
- Patients cannot develop two complications in one model cycle (one year).

Given that risk of death increases over time in the general population and risk of progression in Fabry disease has been observed to increase over time,[46] it is implausible that transition probabilities are constant over time.

In summary, whilst the model structure and general approach are reasonable, the model fails to produce credible results. The greatest deficiency of the model is the structural and parameter assumption of constant transition probabilities that are too low to be realistic. There are further limitations, including a lack of inclusion of kidney transplants. Several ERG analyses and the ERG base case are designed to mitigate some of these flaws (see Section 4.44.4), but not all flaws of the model could be addressed.

4.3.3 Population

The company model considers two patient populations: For the base case analysis, the model uses patients similar to the ATTRACT study population, whilst in a scenario the model uses a hypothetical cohort of Fabry patients aged 16 years at baseline.

The ERG noted there are some differences between the modelled population for the base case analysis and the ATTRACT study population. Whilst the ATTRACT study population consisted of 56% females in the Migalastat group and 57% females in the ERT group respectively, both patient populations in the model consist of 50% males and females, and the CS states this assumption was based on clinical expert opinion. The average body weight of patients is stratified by gender and age with 10-year age intervals starting from age 16, and average weight in each age cohort was based on data from the Health Survey England (HSE)[47] (CS Table D12.4). Hence, the model is predicated on the assumption that Fabry patients have a similar body weight as the average population and this was also based on clinical judgement. A scenario analysis has been performed that uses the average weight of patients enrolled in the ATTRACT clinical trial[20] (74.1 kg).

The ERG found that clinical trials in Fabry disease consistently had patient populations that weighed less than the general population at the same age. In ATTRACT[20] the average patient's body weight was 74.1 kg,[20] with 44% of the overall population male and an average age of 48.9 years. In the general population males aged 45-54 years have a mean weight of 87.7 kg whilst females have a mean weight of 74 kg. When assessing other RCTs in ERT, three other studies reporting patient weights were identified. In a trial of agalsidase beta by Banikazemi and colleagues,[37] 88% of the trial population were male with a mean age of 46.9 years, and a mean weight of 70.1 kg. The mean weight in the general population of males for those aged 45-54 years is 87.7kg.[47] A trial of agalsidase beta by Eng and colleagues,[38] had a 97% male population with mean weight of 68.45 kg at age 30 years. In contrast, the male general population aged 25-34 years has a mean weight of 83 kg.[47] A trial of agalsidase alfa by Schiffman and colleagues[40] had 26 males with a mean weight of 74.83 kg and a mean age of 34.18 years. If these males were the same as the general population, we would expect them to weigh 83 kg.[47] It appears likely that the company base case analysis overestimates the body weight of patients receiving ERT. The company sensitivity analysis assuming patient weight based on the ATTRACT trial is more plausible than assuming patient weight from the general population. We therefore conducted analyses including this assumption in Section 4.4.

Both the ATTRACT and hypothetical patient populations were assigned proportionally to health states of the model at baseline. In the company's base case analysis, this assignment to baseline health states was based on medical history data collected from patients enrolled in the ATTRACT trial, as reported in Table 26~~Table 26~~.

Table 26: Distribution of patients between health states at the start of the model in the company's base case (ATTRACT population) (CS Table D12.5)

Health State	Proportion of patients in state at baseline	Source
Pain	14.0%	Remaining percentage of patients who are not in any of the other starting health states listed in this table
CEFD	63.2%	Patients with a medical history of left ventricular hypertrophy (17/57), abnormal MRI (as a proxy for white matter lesions) (1/57), proteinuria (as a proxy for chronic kidney disease stage 1-4) (18/57) = 36 of 57 patients in ATTRACT
Cardiac complications	21.1%	Patients with a medical history of atrial fibrillation (5/57), cardiac failure (1/57), cardiomyopathy (6/57) = (12 of 57 patients in ATTRACT)
ESRD	0%	1 patient in ATTRACT had a history of renal failure but patients with ESRD would not be started on treatment with migalastat
Stroke	1.8%	Ischaemic stroke (1/57 patients in ATTRACT)

CEFD: clincally evident Fabry disease; ESRD: end-stage renal disease; MRI: magnetic resonance image

For the hypothetical patient cohort with starting age 16 scenario analysis, it was assumed that 80% of patients start in the pain state and 20% in the CEFD state.

The full inclusion and exclusion criteria for the ATTRACT trial are reported in the CS (CS Table C9.4) and the CS states that the patient population *'exhibited the full spectrum of severity of clinical manifestations associated with Fabry disease and are reflective of the expected treatment population in the UK*." (CS page 94). The ERG believes that the inclusion and exclusion criteria of the ATTRACT trial did not affect the validity of the model. However, we

have concerns with respect to the starting distribution across health states in the model. The medical history data from the ATTRACT trial used to allocate patients to starting health states show that the patients had lower rates of events than would be expected according to baseline characteristics for patients registered in the global Fabry registry.[46] Further, as Fabry disease is caused by a mutation of the *GLA* gene which is located on the x-chromosome, x-inactivation (lyonization) may lead to even more varied outcomes and different onset in females as compared to males (e.g. El-Abassi and colleagues[48]). Though the model used gender invariant starting distributions, it is set up in a way which allows defining different starting distributions for males and females. The ERG therefore suggests that the starting proportions of patients in health states should be based on Fabry registry data by Eng and colleagues.[46] The ERG has performed this additional analysis and results are reported in section 4.44.4.

The modelled patient population generally accords with the licensed indication for migalastat, which is for patients who have amenable mutations who are at least 16 years old and do not have ESRD. The modelled patient population is also in accord with the NICE scope, which specifies a population of people with Fabry disease with a confirmed *GLA* mutation that is amenable to migalastat in vitro. The inclusion of subgroups was not specified in the NICE scope and the ERG is not aware of any important subgroups that should have been considered.

4.3.4 Interventions and comparators

The intervention assessed is orally administered migalastat in vitro with a recommended dose in adults and adolescents from 16 years of age of 1 capsule containing 150mg of migalastat hydrochloride (123 mg migalastat) once every other day at the same time of day. As previously stated, no dosage adjustment is required based on age. The comparator included in the company's model is ERT (both agalsidase alfa and agalsidase beta), administered via intravenous infusion once every two weeks. The model assumes that agalsidase alfa is administered at a dose of 0.2mg/kg/infusion and agalsidase beta at a dose of 1mg/kg/infusion. The CS treats both agalsidase alfa and beta as clinically equivalent, based on the view of Biegstraaten and colleagues,[49] who state that "*no studies to date have shown convincing evidence on clinical grounds for superiority or non-inferiority of either one of these enzymes in head to head comparative studies*".

The NICE scope requires the comparison of migalastat with agalsidase alfa and with agalsidase beta. The company uses a blended comparator of both of these (described as ”ERT”) in their model. To account for differences in drug acquisition and administration costs, the model assumes a market share based on clinical expert opinion of 70% for agalsidase alfa and 30% for agalsidase beta respectively. This is broadly consistent with the Fabry Reported Outcomes Survey submitted to this appraisal by the MPS Society as a consultee comment. However, the ERG notes that the comparator chosen in the company model is not in full accord with the NICE scope. Rather, a more appropriate approach to economic analysis in the context of the NICE Guide to the methods of technology appraisal[50] and general economic literature would have been to consider all treatment options in a single incremental analysis comparing each successive alternative from the least costly to the most costly. The ERG therefore performed a fully incremental analysis and results are reported in section 4.44.4. In the view of the large difference in costs between migalastat and ERT, the differences between the costs of individual ERT using a blended analysis are unlikely to be significant.

4.3.5 Treatment effectiveness and extrapolation

The clinical effectiveness parameters used in the model are for disease progression, discontinuations of ERT (due to infusion associated reactions), treatment emergent adverse events (TEAE), and mortality. For the company’s base case analysis, migalastat and ERT are assumed to be clinically equivalent. Note, however, that the total number of patients randomised in the ATTRACT trial (n=60) was inadequate to test for non-inferiority of migalastat compared to ERT based on the two primary outcomes of measured and estimated renal function. The company instead made an assumption that migalastat has ‘comparable’ effectiveness to ERT according to the differences between migalastat and ERT groups in annualised changes in mGFR and eGFR (see section 3.1.6.23.1.6.2). For transitioning between alive states and the ‘death’ state, the model uses either age and gender specific background mortality, or age invariant mortalities as informed by the study of Rombach and colleagues.[1] The CS states that background mortality was taken from UK life tables, stratified by age and gender, though the ERG found that the values used in the model do not accord with those reported by the Office for National Statistics (2012-2014).[11] Disease specific mortality was also taken from the study by Rombach and colleagues,[1] who estimated age invariant mortalities from complication states for men and women separately. For transitioning from symptomatic states to the ‘death’ state of the model, the model chooses the highest value from either the age and gender specific

background mortalities or the age invariant disease specific mortalities. For TEAE, the model uses data about the number of patients experiencing TEAE in the ATTRACT clinical trial. Treatment discontinuation was estimated to be 0.05% for the ERT arm, whilst no treatment discontinuation was assumed for migalastat.

4.3.5.1 Transition probabilities

Transition probabilities between health states are based on the study by Rombach and colleagues,[1] as described in section 11.1 of the CS, and further discussed in section 4.24.2 of this ERG report. Transition matrices for treated/untreated males/females are reported in Tables D12.6 to D12.9 of the CS (pages 191-192) and a summary of yearly transition probabilities based on Rombach and colleagues[1] is presented in Table D12.11 (CS page 195).

Note that Table 27 of the ERG report differs from Table D12.11 of the CS; whilst Table D12.11 confuses transition probabilities for treated and untreated patients, in the model they were used correctly. Further, table D12.11 of the CS reports identical transitions for treated and untreated patients between 2 and 3 complication states and from 2 or 3 complication states to death. However, the study by Rombach et al.[1] and the company's model use different transitions between these states for treated and untreated patients. The ERG has corrected these errors so that Table 26 of the ERG report provides the correct transition probabilities.

In the study by Rombach and colleagues,[1] a decision analytic model was developed based on data from the Dutch Fabry cohort with 116 adults and 26 children. Seventy five patients started ERT treatment and information on disease progression was obtained from medical chart reviews relating to the period before and after the introduction of ERT. Because of the limited data available, Rombach and colleagues[1] used data on disease progression for untreated patients from the period prior to the introduction of ERT and assumed that ERT only reduces the progression to the next disease state. Yearly transition probabilities between the 'alive' states in the model were calculated through Kaplan-Meier survival analysis. These probabilities were adjusted by a relative risk reduction based on the median ERT treatment duration. All transitions between the 'alive' states of the model are assumed to not vary by age, i.e. the same probability applies to each cycle of the model.

Table 27 Summary of clinical variables applied in the company analysis (CS Table D12.11)

Variable	Value	Range or 95% confidence interval	Source
Baseline patient characteristics			
Age	48 years	18 – 72 years	Table C9.7[20]
% female	50%	0 – 100%	Mean from clinical expert opinion, range tested in sensitivity analysis
Body weight	See Table D12.4	N/A	Health & Social Care Information Centre, 2014
Transition probabilities – treated males			
Pain > CEFD	0.0711	0.002-0.2409	Rombach et al., 2013[1]
CEFD > ESRD	0.0017	0.000-0.0059	
CEFD > cardiac	0.0085	0.0002-0.0324	
CEFD > stroke	0.0029	0.0001-0.0108	
CEFD > death	0.0006	0.000-0.0022	
Transition probabilities – treated females			
Pain > CEFD	0.1018	0.0028-0.3216	Rombach et al., 2013[1]
CEFD > ESRD	0.0016	0.000-0.0065	
CEFD > cardiac	0.00623	00002-0.0268	
CEFD > stroke	0.0024	0.0001-0.0093	
Transition probabilities – treated males and females			
ESRD > ESRD + cardiac	0.0086	0.0002-0.0316	Rombach et al., 2013[1]
ESRD > ESRD + stroke	0.0063	0.0002-0.026	
ESRD > death	0.0109	0.0003-0.0425	
Cardiac > cardiac + ESRD	0.005	0.0001-0.0186	
Cardiac > cardiac + stroke	0.0077	0.0002-0.0285	
Cardiac > death	0.0134	0.0003-0.0519	

continued

Table 27 – continued

Variable	Value	Range or 95%	Source

		confidence interval	
Stroke > stroke + ESRD	0.0045	0.0001-0.0168	
Stroke > stroke + cardiac	0.0094	0.0002-0.0321	
Stroke > death	0.012	0.0003-0.0397	
2 complications > 3rd complication	0.1379	0.0216-0.3506	
2 complications > death	0.4068	0.1512-0.7009	
3 complications > death	0.4068	0.1327-0.6961	
Transition probabilities – untreated males			
Pain > CEFD	0.0711	0.0019-0.2354	Rombach et al., 2013[1]
CEFD > ESRD	0.002	0.0000-0.0076	
CEFD > cardiac	0.0097	0.0003-0.0354	
CEFD > stroke	0.0034	0.0001-0.0127	
CEFD > death	0.0006	0.0000-0.0021	
Transition probabilities – untreated females			
Pain > CEFD	0.1018	0.0025-0.3781	Rombach et al., 2013[1]
CEFD > ESRD	0.0018	0.0000-0.0072	
CEFD > cardiac	0.0071	0.0001-0.0275	
CEFD > stroke	0.0027	0.0001-0.0097	
Transition probabilities – untreated males and females			
ESRD > ESRD + cardiac	0.0133	0.0004-0.0462	Rombach et al., 2013[1]
ESRD > ESRD + stroke	0.0098	0.0002-0.0344	
ESRD > death	0.0169	0.0004-0.0648	
Cardiac > cardiac + ESRD	0.0077	0.0003-0.0316	
Cardiac > cardiac + stroke	0.0118	0.0006-0.0526	
Cardiac > death	0.0206	0.0008-0.0706	
Stroke > stroke + ESRD	0.0007	0.0002-0.0266	
Stroke > stroke + cardiac	0.0146	0.0003-0.062	
Stroke > death	0.0186	0.0005-0.0655	
2 complications > 3rd complication	0.1379	0.0167-0.3565	
2 complications > death	0.4068	0.1438-0.7065	
3 complications > death	0.4068	0.1228-0.6943	

CEFD: clinically evident Fabry disease; ESRD: end-stage renal disease

A different approach was taken for transitions from the 'alive' states to the 'death' state of the model. According to the CS, background mortality in the model was informed by UK life tables

(Office for National Statistics, 2014),[51] and unlike any other transition probability in the model, background mortality is also stratified by age (annual probabilities to transition into the dead state) and gender. However, age and gender specific mortality estimates were only used in the model if they exceeded the respective mortality estimates for symptomatic patients as reported by Rombach and colleagues.[1] Mortality estimates from Rombach and colleagues[1] were stratified by gender but are age invariant, that is, the same annual probability of death was used for a complication state as long as it exceeded the respective age dependant background mortality.

The ERG has concerns about the annual transition probabilities used in the model. Transition probabilities were estimated from a Dutch Fabry cohort, which may differ in population characteristics to both the ATTRACT trial cohort and the hypothetical cohort aged 16 at baseline that were used in the model. This, and the life-table data used in the model, may have led to an unrealistically high life expectancy. As neither the CS nor the study by Rombach and colleagues[1] reports odds ratios or relative risk reductions due to ERT, it was not possible to re-calculate transition probabilities with treatment for the ATTRACT patient cohort or the hypothetical population aged 16 years at baseline. The ERG conducted a scenario analysis that applied a multiplier to all transition probabilities except those moving from any multi-complication state and background mortality. This analysis calibrated the model against the expected life expectancy in Fabry patients. Full methods and results of this analysis are reported in section 4.44.4 of this report.

Further, the ERG has strong concerns about the mortality estimates used in the company's model. Firstly, it appears that values for background mortality estimates used in the model are unrealistically low. The ERG compared the background mortality used in the model with that reported by the Office for National Statistics (2012-2014),[11] and found that the data used in the model did not match the data reported by the ONS. Rather, the background mortality data used in the model seem to substantially underestimate mortality, which partly explains why the model submitted by the manufacturer has unexpectedly high life expectancy. The ERG has therefore conducted a scenario analysis by using ONS mortality data from 2012-2014. Results of this scenario are reported in 4.44.4 of this report and show that this reduces the life expectancy to a more realistic level. Another strong concern with respect to mortalities is that the model uses age invariant mortalities as reported by Rombach and colleagues[1] whenever they exceed respective age dependant background mortalities. A more reasonable approach would have

been to use excess mortality from complications which varies by age and to add this to time and gender variant background mortality. However, it was not feasible for the ERG to source respective data on excess mortalities for complication states and to reconfigure the model.

4.3.5.2 Treatment emergent adverse events

Treatment emergent adverse events (TEAE) are discussed in section 12.2.4 of the CS and summarised in Table D.12.10 (CS page 194). Note that the ERG and NICE requested clarification from the company regarding the source of TEAE in the CS and also how annual probabilities for TEAE were calculated. The company clarified (question B7) that the correct source of data for the number of patients experiencing TEAE in the ATTRACT study[20] is table C9.27 (page 122) of the CS. Annual probabilities for TEAE were calculated using the number of patients experiencing events in the ATTRACT safety population (n=21 in the ERT arm and n=36 in the migalastat arm) and adjusting this for exposure (476.67 days in the ERT arm and 522.19 days in the migalastat arm). The company's response also included correction of a typographical error to table D.12.10, which led the ERG to recalculate the annualised probabilities of dyspnoea and urinary tract infection (Table 28~~Table 28~~).

Note that when the ERG calculated the annual probabilities for TEAE, we obtained slightly different results to those reported in Table 28~~Table 28~~ below. However, changing these probabilities led to negligible differences in outcomes (−£64 versus −£62 for the adverse events cost).

Table 28: Annual probability of TEAE (from CS Table D12.10 and Table 3 in company's clarification response B7)

	Number of patients with event in study		**Annual probability after adjustment for exposure**	
	Migalastat	ERT	Migalastat	ERT
Headache	9	5	18.2%	18.8%
Influenza	5	4	9.9%	14.9%
Dyspnoea	1	2	2.0%	7.4%
Upper respiratory tract infection	4	1	7.9%	3.7%
Urinary tract infection	4	1	7.9%	3.7%
Gastritis	1	2	2.0%	7.4%

The ERG notes that the adverse events included are those TEAE with more than 10% of either the ERT or migalastat arms and it was not reported if any of these events were serious adverse events.

4.3.5.3 Treatment discontinuation

The model considers discontinuations of patients from ERT due to infusion associated reactions (IAR). Discontinuations are discussed in section 12.2.1 of the CS and are based on published evidence. The company states that Banikazemi and colleagues[37] estimated discontinuation of patients from ERT at 1% annually. However, the company states that this rate may be high because IAR can be controlled in a clinical setting through additional medications. Discontinuation was therefore assumed by the company to be 0.05% per annum for ERT patients.

When the ERG reviewed Banikazemi and colleagues,[37] we found that in the trial three patients out of 30 in the ERT arm were withdrawn from the trial due to infusion related adverse events. None of these patients permanently discontinued treatment. One patient continued on treatment but was monitored for safety, and the other two patients successfully resumed therapy later and successfully continued treatment. Clinical advice we have received indicates that the discontinuation rates may be too low for ERT. However, given the lack of data available to confirm this, we have not modified the discontinuation rate for ERT in the ERG analyses reported in Section 4.4.

Clinical advice to the ERG and the consultee submissions for this appraisal from the Royal Free London Hospital and the Queen Elizabeth Hospital Birmingham indicated that patients may not be fully compliant and that some patients may discontinue migalastat due to lack of benefit. A scenario analysis was conducted by the ERG to address this by assuming that migalastat has an equivalent discontinuation rate to ERT. Results of the ERG's scenario analysis are reported in section 4.44.4.

4.3.6 Health related quality of life

The model assigns HRQoL utility scores to each health state. Over the course of disease progression, HRQoL deteriorates as patients transition to worse health states with an increasing

number of major complications. AE and infusion-related disutilities are applied in the form of utility decrements.

The company conducted a systematic review of quality of life studies for patients with Fabry disease that identified four studies.[1, 52-54] The health state utility values used in the company model were derived from the Dutch cohort study by Rombach and colleagues.[1] These values were collected using the EQ-5D questionnaire, with the UK tariff, completed by 57 patients treated with ERT. Four disease states were defined from the Dutch cohort study: asymptomatic, acroparasthesia/symptomatic, single complication state, and multiple complications state (CS Table C10.1, page 141).

The utility values used in the company's model follow a similar structure (see Table 29~~Table 29~~): pain/CEFD, defined as a symptomatic state; single-complication states that include ESRD, cardiac complications, and stroke; and multiple complications states including ESRD + cardiac, cardiac + stroke, ESRD + stroke, and ESRD + stroke + cardiac. The company also ran scenario analyses using alternative utility estimates from Miners and colleagues[53] and Gold and colleagues[52] The model results were unchanged using these alternative scenarios as the company assumed that migalastat and ERTs are clinically equivalent.

AE disutilities in the model were taken from a study by Sullivan and colleagues[55] study and were obtained using the EQ-5D questionnaire. Sullivan and colleagues[55] reported an "off-the-shelf" catalogue for chronic conditions of EQ-5D preference weights using the UK-based tariff for the valuation (Table 30~~Table 30~~). The duration of the AE is based on assumptions and varies between 1 day for headache and 5 days for influenza per year.

Table 29 Summary of utility values for health states in the cost consequence model (CS Table C10.2)

State	Utility value	Lower bound	Upper bound	Health state from Rombach et al.[1]
Pain	0.762	0.699	0.822	Acroparesthesia/ Symptomatic
CEFD	0.762	0.699	0.822	
ESRD	0.744	0.658	0.821	Single complication
Cardiac complications	0.744	0.658	0.821	
Stroke	0.744	0.658	0.821	
ESRD + Cardiac	0.584	0.378	0.790	Multiple complications
Cardiac + Stroke	0.584	0.378	0.790	
ESRD + Stroke	0.584	0.378	0.790	
ESRD + Stroke + Cardiac	0.584	0.378	0.790	
Death	0	N/A	N/A	

CEFD: Clinically evident Fabry Disease, ESRD: end-stage renal disease

Table 30 Summary of adverse event disutilities used in the cost-consequence model (Table C10.4)

Event	Utility value	Lower bound	Upper bound	Source
Headache	−0.078	−0.088	−0.068	Sullivan et al.[55] (migraine)
Influenza	-0.162	-0.194	−0.130	Turner et al., 2003[56]
Dyspnoea	−0.090	−0.116	−0.064	Sullivan et al.[55] (other respiratory)
Upper respiratory tract infection	-0.018	−0.027	−0.010	Sullivan et al.[55] (chronic sinusitis)
Urinary tract infection	−0.053	−0.069	−0.037	Sullivan et al.[55] (urinary tract disorder)
Gastritis	−0.130	−0.161	−0.099	Sullivan et al.[55] (gastritis and duodenitis)

Infusion-related utility decrements were based on a discrete choice experiment (DCE) conducted by Lloyd and colleagues,[57] which explored the value of moving to an oral therapy. A sample of 506 people from the UK general population was used. The DCE gave a −0.053 decrement for self- administered and a −0.050 decrement for nurse-administered infusions. The base case model only included utility decrements for the mode of administration. These did not include disutilities for infusion associated reactions, headaches, or antibody formation.

We note that the differences in HRQoL in the model results are mainly attributable to utility decrements due to infusion for the ERT treatment and, to a lesser extent, to differences in AE, as the company has assumed that migalastat and ERT are clinically equivalent with respect to the incidence of major complications.

The ERG has four major criticisms of the utility values used in the economic model. Firstly, there is a lack of face validity in the values chosen for the model. The values chosen suggest that the disutility associated with developing ESRD for patients with CEFD (−0.018) is less than the disutility associated with ERT infusion (−0.05). This seems unlikely. Secondly, there are problems with assuming that ESRD, cardiac complications and stroke all have the same utility value, as there are large differences in the quality of life for these complications. Thirdly, these utility values have been based upon a small number of patients. Finally, the disutilities for infusions have been collected using a discrete choice experiment and it is unclear how comparable estimates from DCE are to those derived using the EQ-5D.

The ERG has conducted a search for utility studies for patients with ESRD. We identified a meta-analysis by Liem and colleagues[58] for quality of life of patients with ESRD, including studies using EQ-5D. The meta-analysis found that for ESRD patients on haemodialysis, the mean utility value was 0.56. We suggest this utility value would be a better estimate for patients with Fabry disease who have ESRD, rather than the estimate used in the company model. For the estimates for stroke and cardiac complications, we consider that the estimates from Miners and colleagues[53] have more face validity and are more consistent with people in the general population with stroke and cardiac complications. Miners and colleagues[53] collected EQ-5D utility values for 38 patients in UK with Fabry disease. The values are reported as a disutility for stroke (−0.28) and cardiac symptoms (−0.20).

We have also conducted a search for utility studies for patients receiving infusions. We identified a study by Matza and colleagues[59] that estimated the disutility associated with an injection, 30 minute infusion and 2 hour infusion in 121 participants from the UK general population. The study used time trade-off questionnaires and found the 30 minute infusion and 2-hour infusion once a month to have mean disutilities of −0.02 and −0.04 respectively. The utility values from this study appear to be consistent with the utility values from the company's DCE. However the ERG still has concerns about how consistent these utility values are compared with health state values using EQ-5D. The ERG considers a better approach, more consistent with the reference case, would have been to collect EQ-5D values from the company's clinical trial for patients receiving ERT and migalastat. Our opinion is that the disutility estimate would be lower than seen in the discrete choice experiment. This view is based on considering the magnitude of disutility from the adverse events for this and other appraisals. We have investigated running the model with a lower disutility in section 4.44.4.

Overall the ERG has several concerns relating to the utility values used in the model by the company. In particular the utility values for the health states of ESRD, cardiac complications and stroke lack face validity and we have suggested more plausible alternative values and report scenario analyses for these changes in section 4.44.4.

4.3.7 Resource use and costs

The model included costs for drugs and administrations, treatment of adverse events and health states. The company literature search included inclusion criteria for costs but the CS does not report the results of any studies found. The company based their estimation of the frequency of resources needed to treat Fabry disease on those in the study by Rombach and colleagues[1]

4.3.7.1 Drug acquisition costs

Costs for drug acquisition consist of drugs and administrations Migalastat is an oral treatment taken once every two days and will be available in a pack with 14 capsules at a list price of £16,153.85 per pack (£210,000 per year). The cost of ERT was taken from the BNF and is shown in Table 31~~Table 31~~. The CS states that ERT is associated with a confidential discount to the NHS and has assumed this discount is 3%. Results are presented based on this assumed discounted price. ERT is administered once every two weeks as either agalsidase beta or

agalsidase alfa at 1mg / kg and 0.2 mg / kg respectively. The company assumes that the number of vials per person is rounded up to the nearest vial.

Table 31 Dosage and cost of ERT (CS Table D12.12)

	Vial size	Cost per vial	Cost per vial used in the model[a]	Dose per infusion (mg per kg)
Agalsidase beta	5 mg	£315.08	£305.63	1
	35 mg	£2,196.59	£2,130.69	
Agalsidase alfa	3.5 mg	£1,068.64	£1,036.58	0.2

[a] Company assumes a 3% confidential discount to the NHS

The average weight by age group and gender is taken from The Health Survey for England (CS Table D12.4).[47] The company assumes that the market share of English patients receiving ERT that have agalsidase alfa is 70% and the remainder have agalsidase beta. This was similar to the market share reported in the Fabry Reported Outcomes Survey (based on 128 Fabry patients) by the MPS Society consultee submission to NICE. The cost of ERT by age and gender is shown in Table 32~~Table 32~~.

Table 32 Cost of ERT infusion by age and sex (CS Table D12.14)

Age	Cost per infusion for male patients			Cost per infusion for female patients		
	Agalsidase beta	Agalsidase alfa	ERT Cost	Agalsidase beta	Agalsidase alfa	ERT Cost
16-24	£4,873	£5,183	£5,090	£3,964	£4,146	£4,092
25-34	£5,178	£5,183	£5,182	£4,567	£5,183	£4,998
35-44	£5,484	£5,183	£5,273	£4,567	£5,183	£4,998
45-54	£5,484	£6,219	£5,999	£4,567	£5,183	£4,998
55-64	£5,484	£6,219	£5,999	£4,567	£5,183	£4,998
65-74	£5,178	£5,183	£5,182	£4,567	£5,183	£4,998
75+	£5,178	£5,183	£5,182	£4,270	£4,146	£4,183

ERT is administered either by a nurse or is self-administered. The CS assumes, based on clinical opinion, that 50% of patients self-administer and only have one nurse visit per year, and the other 50% require a nurse to deliver each infusion. Infusion time varies between 40 minutes

for agalsidase alfa and 2 hours for agalsidase beta and both infusions require a further 45 minutes to prepare and clean / up. Nurse visit costs were estimated at £91 per hour, based on PSSRU.[60] The cost per administration for a nurse-led infusion was an average of £165.60. For patients who self-administer, there is a delivery and collection charge of medication and disposables estimated at £200 per infusion (i.e. every 2 weeks) based on clinical expert opinion. The CS states that this service has been contracted by NHS England under a confidential national tender. Clinical advice to the ERG suggested that there is another method of administration of ERT (not considered in the company model), whereby semi-independent patients have a nurse set up the infusion and then go away and the patients would take it down themselves at the end. This method saves a lot of 'nurse time' with agalsidase beta in particular.

4.3.7.2 Health state costs

Health state costs consisted of costs to treat acute events, which occur once as a patient transitions into each state, and ongoing follow up costs, health care contacts and diagnostic, laboratory and imaging tests (which are applied every cycle that the patient remains in the state). These costs are shown in Table 33~~Table 33~~ for each category.

For acute events (hospitalisations), unit costs were taken from the NHS reference costs 2014-15,[61] derived from a range of HRG codes representing different severity for each event, weighted by the number of Finished Consultant Episodes from the NHS reference costs (CS D12.16).

Healthcare contacts cost includes the costs of contact with health professionals, such as GPs, physiotherapists, psychiatrists and social workers, although it does not include the cost of any outpatient appointment with a hospital consultant specialist for Fabry disease. Clinical advice to the ERG suggests that each patient would see a hospital consultant twice a year. The frequency of healthcare visits was taken from Rombach and colleagues[1] (CS Table D12.17), assuming that these will not be significantly different from those in the UK. Clinical advice to the ERG considered that there would be similar resources used in The Netherlands and the UK to treat patients with Fabry disease. The cost for health care contact time is based upon the cost per hour of contact according to the PSSRU.[60] The duration of an average GP visit is 11.7 minutes and the duration of other health profession visits / consultations were assumed to be an hour.

Table 33 List of health states and associated costs in the cost-consequence model (CS Table D12.21)

Health states	Items	Value
Pain	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£490.35
CEFD	Hospitalisation	£1,630.30
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£450.28
ESRD	Hospitalisation	£3,062.87
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£856.36
	Complication follow-up costs	£25,800.84
Cardiac complications	Hospitalisation	£1,578.13
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£856.36
	Complication follow-up costs	£627.09
Stroke	Hospitalisation	£2,906.77
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£856.36
	Complication follow-up costs	£415.62
ESRD + Cardiac	Hospitalisation	£4,641.00
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£544.52
	Complication follow-up costs	£26,427.93
Cardiac + Stroke	Hospitalisation	£4,484.90
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£544.52
	Complication follow-up costs	£26,216.46
ESRD + Stroke	Hospitalisation	£5,969.64
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£544.52
	Complication follow-up costs	£627.09
ESRD + Cardiac + Stroke	Hospitalisation	£7,547.77
	Diagnostic, laboratory and imaging tests	£562.76
	Healthcare contacts	£544.52
	Complication follow-up costs	£26,843.55

The frequency of diagnostic, laboratory and imaging tests for all patients with Fabry disease were taken from the Adult Fabry Disease Standard Operating Procedure[62] (CS Table D12.19), with the unit costs taken from the NHS reference costs[61] (CS Table D12.19). Diagnostic tests include blood and urine tests, MRI, angiogram, echocardiogram and ECG. The same cost of £562.76 per year was applied to patients in each health state (Table 33~~Table 33~~).

Follow-up costs for the health states associated with cardiac complications, ESRD and stroke are shown in Table 33~~Table 33~~. The cost for cardiac complications is based upon the cost per patient with CHD in the UK in 2015 from a study by Bhatnagar and colleagues.[63] The cost for ESRD is estimated assuming dialysis is needed 3 times a week. The cost of stroke is based on the annual cost of post-acute care for stroke survivors.[64] The ERG notes that the cost of these health states is derived from treating a mixed group of people with these complications, rather than patients with Fabry disease with this complication. As there may be differences to the manifestations of patients with Fabry disease with cardiac complications and people with coronary heart disease, there may be some differences in the treatment costs between these groups. Expert advice to the ERG indicated that the cardiac symptoms experienced by patients with Fabry disease differ from coronary heart disease and includes pacemakers and cardiomyopathy. However the ERG considers that any differences are unlikely to affect the model results.

4.3.7.3 Adverse event costs

The adverse event costs were for the treatment for each specific adverse event. The following adverse events were included headache, influenza, upper respiratory tract infection, urinary tract infection, and gastritis. The costs are shown in Table 34~~Table 34~~.

Table 34 List of adverse events and summary of costs included in the model (CS Table D12.22)

Adverse events	Items	Value
Headache	Paracetamol	£0.06
Influenza	Decongestant, GP visit	£47.28
Dyspnoea	GP visit	£43.88
Upper respiratory tract infection	Paracetamol, GP visit	£44.06
Urinary tract infection	Amoxicilin, GP visit	£44.78
Gastritis	Omeprazole, GP visit	£44.93

The company varied the costs by +/- 20% in the deterministic sensitivity analyses. The ERG notes that the total health state costs, diagnostic and healthcare contact costs were the same in the ERT and migalastat analyses and changes to these costs in the deterministic sensitivity analyses had no effect on the model results. Furthermore, these costs were small relative to the acquisition costs of ERT and migalastat, contributing about 1% of the overall costs of treating these patients.

4.3.7.4 Cost effectiveness Results

The results of the *de novo* cost-consequence analysis are presented as costs, life-years, and QALYs. Table 35~~Table 35~~ reports incremental cost and QALY results for ERT and migalastat. Table 36 (CS Table D12.27, page 214) reports life-year and QALY results and Table 37~~Table 37~~ (CS Table D12.30, page 215) reports cost results from the company base case analysis. The company assumed a 3% price discount for both ERT therapies in their cost analysis. In addition to aggregate results, the company submitted a table providing QALYs by health states (Table D12.28, page 214) and utility-decrement-generating events (adverse events, infusions). The infusion disutilities were responsible for virtually all (0.97 of 0.98 QALYs) of the differences between migalastat and ERT, as the efficacy was assumed equivalent between migalastat and ERT.

Table 35 Base case cost-consequence analysis results (ERT 3% price discount)

Intervention	**Costs (£)**	**Incremental Costs (£)**	**QALYs**	**Incremental QALYs**
ERT	2,581,037		13.36	
Migalastat	4,024,050	1,268,674	14.33	0.98

Table 36 Company base case deterministic analysis, life-years and QALYs (CS Table 12.27)

Outcome	**Migalastat**	**ERT**	**Difference**
QALYs (undiscounted)	26.70	24.88	1.82
QALYs (discounted)	14.33	13.36	0.98
LYs (undiscounted)	35.43	35.42	0.01
LYs (discounted)	19.00	19.00	0.00

As can be seen in Table 36, the estimated overall survival is 35.4 years from the starting age for migalastat, producing estimated life-expectancy of 83.4 years in Fabry patients who receive migalastat. The estimate for ERT is similar with life expectancy only 0.01 years less. We consider that the predicted life expectancy is much higher than would be expected in a cohort of Fabry disease.

Table 37 Costs in the company base case (CS Table D12.30) (ERT 3% price discount)

Health state	Cost migalastat (£)	Cost ERT (£)	Increment (£)	Absolute increment	% absolute increment
Treatment costs	3,989,923	2,581,037	1,408,886	1,408,886	91%
Administration costs	0	140,149	-140,149	140,149	9%
Diagnostics, Laboratory and Imaging	10,692	10,691	1	1	0%
Hospitalisation costs	678	679	-1	1	0%
Health state follow-up costs	11,709	11,711	-2	2	0%
HCP contacts	10,792	10,790	2	2	0%
Adverse events	255	320	-64	64	0%
Total	**4,024,050**	**2,755,377**	**1,268,674**	**1,549,106**	**100%**

The company presented the results of the model without any specific conclusions or recommendations.

4.3.8 Model validation

This section contains an evaluation of internal consistency (correctness of coding and construction), and external consistency (comparison to external data) in the company model.

4.3.8.1 Internal consistency

The company indicated that the internal consistency of the model was checked by internal and external review for technical correctness. No other evaluations of consistency or validity were undertaken. The ERG examined the code of the model, checked that visual basic macros ran

correctly, ensured that parameters were consistent with their sources, and ensured that the results reported in sensitivity analyses were replicable and correct. The model is technically correct except for some errors in transcription of utility values from Miners and colleagues[53] and Gold and colleagues,[52] both studies that were used in sensitivity analyses that had no effect on incremental costs or QALYs.

An additional problem in the model relates to consistency with the cited source for background mortality. We checked the data listed in the company model and found that it did not match ONS data for 2012-2014.[11] After approximately cycle 30 in the model (age 78), mortality rates were slightly over half those in ONS data for England and Wales.[11] We conducted a sensitivity analysis that corrected the erroneous ONS background mortality data.

4.3.8.2 External consistency

As indicated above the company conducted no analysis of external validity, cross validity, predictive validity or face validity. The model was derived from another model, so external validity checks should begin with an analysis of whether company model is consistent with the model it is based on, Rombach and colleagues.[1] Given the small amount of data that the trials contain, and the small number of patients that were used to parameterize the Rombach model, validating the findings of those models with external data should be done. The ERG have explored whether the findings of either model appear valid compared to larger external datasets.

Given that cross-validation and assessment of predictive validity would require acquiring large datasets or rebuilding existing models, the ERG has not conducted these analyses. The ERG analyses focus on external and face validity of the company model.

Comparing the final outputs; costs, life-years, and QALYs, of the ERT arms of the Rombach model and the company model was not possible, as the company model begins at age 48 and the Rombach model begins at birth. Additionally, the Rombach model does not report life expectancy or life-years as outcomes. These differences mean that it is impossible to isolate comparable final outcomes from the models, even if final age of patients is set to the same and discounting assumptions are equivalent.

The ERG compared the company's predicted life expectancy with published estimates. The company's estimated life-expectancy is 83.4 years in Fabry patients who receive migalastat. The estimate for ERT is similar with life expectancy only 0.01 years less. Comparing both of these values to life-expectancy at birth of individuals born between 2012 and 2014 in the latest ONS statistics, it is evident that the model has a serious external and face validity problem: ONS estimates for 2012-14 report that expected life expectancy is 79.3 years for males and 83.0 years for females in the general population. According to the model, the average Fabry disease patient on migalastat or ERT will outlive the average woman in the general population by about 5 months. The large international Fabry Registry[10] estimates a male life expectancy at birth of 58.2 years and a female life expectancy at birth at 74.8 years.

The ERG observed that the base case analysis' distribution of patients in the starting complication states (cardiac complications and stroke) in ATTRACT may underestimate Fabry disease severity. Table 38 presents a comparison of Fabry Registry data from Eng and colleagues[46] to ATTRACT for males and females. It appears likely that stroke is underestimated by the model in Fabry patients and it is possible that the model underestimates cardiac complications in males. Additionally, Table 38 shows that patients had events at an earlier time than the starting distribution of the model would estimate. The ERG conducted a sensitivity analysis incorporating values from Eng and colleagues[46] and starting patients at an earlier age to correct these discrepancies (section 4.44.4).

Table 38 Starting complication states in the company base case compared to the Fabry Registry[46]

	Cardiac Complications		Stroke	
Population Group	Age at event (mean)	Proportion with event	Age at event (mean)	Proportion with event
Males				
Model	48	21.1%	48	1.8%
Eng et al. 2007[46]	41	19%	38	7%
Females				
Model	48	21.1%	48	1.8%
Eng et al. 2007[46]	47	14%	43	5%

The ERG notes that the migalastat SmPC states that migalastat is not recommended in patients with ESRD, whilst the model allows patients with ESRD to continue treatment with migalastat. The ERG corrected this inconsistency through a sensitivity analysis (section 4.44.4).

4.3.8.3 Summary of ERG view on the company's model validity

The company's assumptions about starting health states underestimate disease severity and progression. The model fails external validity checks and lacks face validity. The ERG conducted scenario analyses (see section 4.44.4) to address the underestimation of disease severity in starting health states, correct erroneous ONS survival estimates, and address underestimation of transition probabilities over time in the model.

Additionally, migalastat is not recommended for use in patients with ESRD. The ERG ran a scenario analysis in which patients discontinue migalastat when they develop ESRD.

4.3.9 Assessment of Uncertainty

This section reports the results of sensitivity analyses, scenario analyses, and a probabilistic sensitivity analysis which were undertaken by the company. All analyses conducted by the company assumed a 3% discount for agalsidase alfa and agalsidase beta.

4.3.9.1 One-way sensitivity analyses

The company undertook a variety of deterministic one-way sensitivity analyses. Values were varied within the upper and lower 95% confidence limits or ranges as indicated in ERG Table 27 (CS Table D12.11, page 195) and in Table 39 below (CS Table D12.24, page 208)

Table 39 Parameters varied in one-way sensitivity analyses (CS Table D12.24)

Parameters	Base case	Lower	Upper
% females	50%	0%	100%
Discontinuation: ERT patients	0.05%	0%	1.0%
Discontinuation: migalastat	0%	0%	0.1%
Annual risk of AE: ERT (± 20% of base case)	100%	80%	120%
Annual risk of AE: migalastat (± 20% of base case)	100%	80%	120%
Discount rate for costs	3.5%	0%	6%

continued

Table 39 – continued

Parameters	Base case	Lower	Upper
Discount rate for outcomes	3.5%	0%	6%
Acute event cost: CEFD	£1,639.03	£1,311.22	£1,966.83
Acute event cost: cardiac complications	£1,578.13	£1,262.51	£1,893.76
Acute event cost: ESRD	£3,062.87	£2,450.29	£3,675.44
Acute event cost: stroke	£2,906.77	£2,325.42	£3,488.13
Adverse event costs (± 20% of base case)	100%	80%	120%
Cost of health care provider contacts (± 20% of base case)	100%	80%	120%
Annual follow-up cost: all patients with Fabry disease	£562.76	£450.21	£675.32
Annual follow-up cost: cardiac complications	£627.09	£501.67	£752.51
Annual follow-up cost: ESRD	£25,800.84	£20,640.67	£30,961.01
Annual follow-up cost: stroke	£415.62	£332.50	£498.74
Market share of agalsidase alfa vs. agalsidase beta	70%	0%	100%
Utility: Pain	0.762	0.699	0.822
Utility: CEFD	0.762	0.699	0.822
Utility: ESRD	0.744	0.658	0.821
Utility: Cardiac complications	0.744	0.658	0.821
Utility: Stroke	0.744	0.658	0.821
Utility: Multiple complications	0.584	0.378	0.79
Disutility per infusion	−0.052	−0.059	−0.045
Disutility: headache	−0.08	−0.09	−0.07
Disutility: influenza	−0.16	−0.19	−0.13
Disutility: dyspnoea	−0.09	−0.12	−0.06
Disutility: upper respiratory tract infection	−0.02	−0.03	−0.01
Disutility: urinary tract infection	−0.05	−0.07	−0.04
Disutility: gastritis	−0.13	−0.16	−0.10
Duration of AE: headache	1	1	2
Duration of AE: influenza	5	3	7
Duration of AE: dyspnoea	3	1	5
Duration of AE: upper respiratory tract infection	3	1	5
Duration of AE: urinary tract infection	2	1	3
Duration of AE: gastritis	3	1	5

CEFD: clinically evident Fabry disease; ESRD: end-stage renal disease

The results of the one-way sensitivity analyses are reported as tornado diagrams separately for costs in Figure 9 (CS Figure D12.7, page 219) and QALYs in Figure 10 (CS Figure D12.6, page 219). The company concluded that the most influential parameters were discount rates, transition probabilities for treated patients, discontinuation rates, the disutility of infusions, and market shares of ERT. The ERG concurs, but would also add that the ranges tested in one-way sensitivity analyses for transition probabilities are insufficient to cover the validity gap between model survival and expected survival,[10, 11] and we would emphasise the importance of disutilities for infusions, as these make up virtually all of the difference in QALYs between migalastat and ERT.

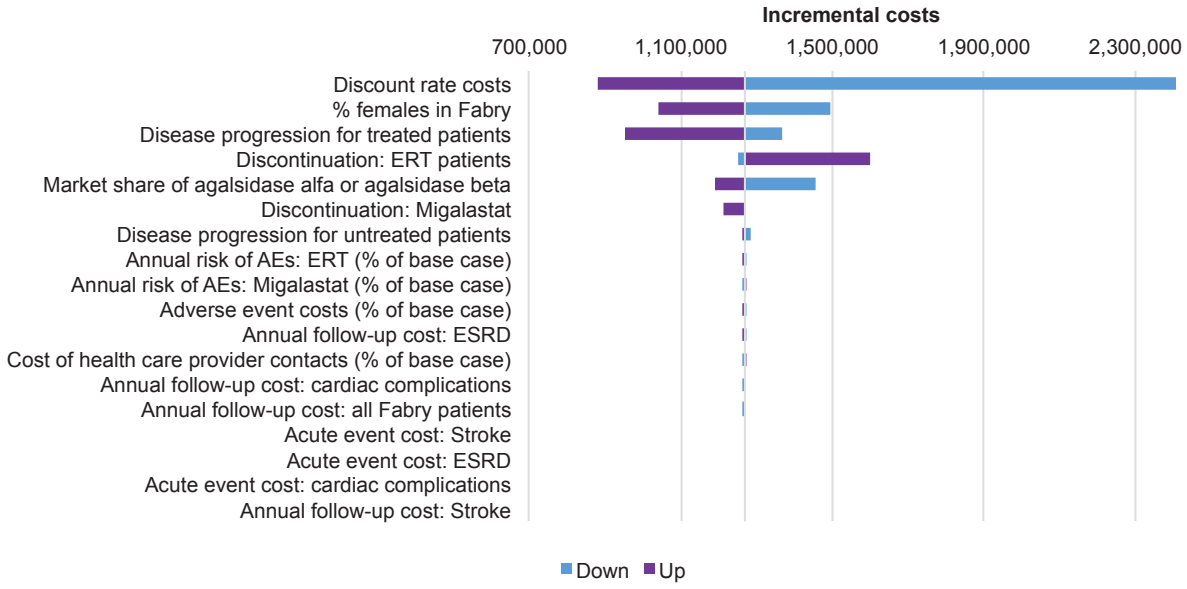

Figure 9 Tornado diagram illustrating cost differences in company one-way sensitivity analyses (CS Figure 12.7)

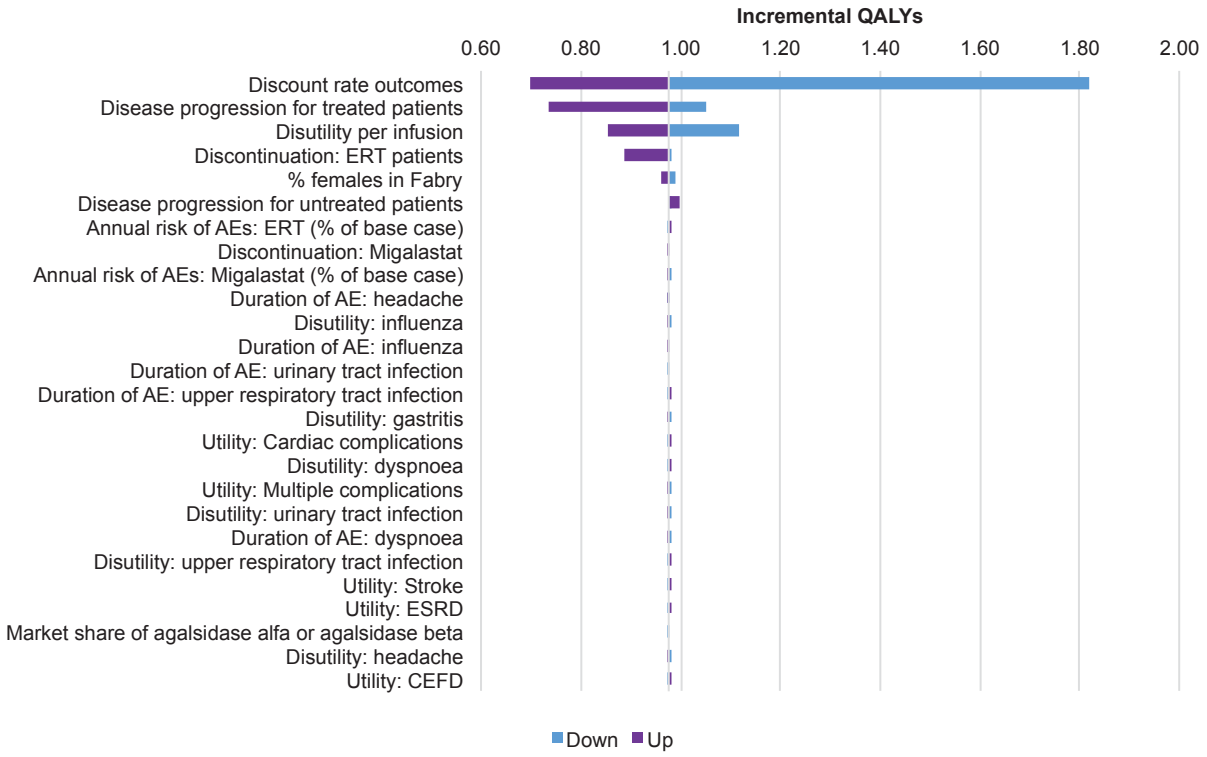

Figure 10 Tornado diagram illustrating QALY differences in company one-way sensitivity analyses (CS Figure 12.6, p219)

4.3.9.2 Scenario Analyses

The company conducted a set of scenario analyses in 10 categories. The CS lists these scenarios, provides justifications and describes their methods (CS pages 207-8). Table 40 lists these analyses and their assumptions.

The ERG was able to check and confirm most scenario analyses within the model. However, the mechanisms for conducting the analyses were not built into the model, requiring all scenario analyses to be manually run. The analyses that used alternative utility values transposed the results for alternative utility sources, i.e. the values presented for Gold and colleagues[52] were derived from Miners and colleagues[53] and vice versa. The ERG was also unable to calculate the alternative utility given for having multiple complications; there appears to be an error in the calculation or in the description of the calculation for these utility values. The results of the scenario analyses are reported in Table 41 (CS Table D12.33, page 220) and Table 42 (CS Table D12.34, page 221).

Table 40 Scenario analyses conducted in the company submission (CS pages 207-8)

#	Analysis	Description
1	ERT price discounts	Price discount for ERT varied: 0%, 5%, 7%. Company base case is 3%.
2	Alternative utility scores	Utility scores from Miners et al. 2002 and Gold et al. 2002 used.
3	Reduced ERT efficacy due to neutralising antibodies	Assumed that ERT patients had a 0.77% probability of discontinuation in the first five years of the model.
4	Age 16 at baseline	Assumed starting age of 16 with 80% in pain state and 20% in CEFD.
5	ATTRACT average body weight	Used mean body weight from the ATTRACT trial (74.1 Kg) for calculating ERT treatment costs
6	Societal perspective	Productivity losses for patients and carers included
7	Greater migalastat effectiveness	Applied 0.66 relative risk to migalastat on-treatment transition probabilities
8	20 year time horizon	Time horizon reduced to 20 years (base case is 41 years)
9	Alternative infusion disutilities	Quoted from the company submission (CS page 208): 1. *Including full surveyed population (not specifically excluding the 53 people that failed the response check)* 2. *Including disutilities for all attributes surveyed (mode of administration, infusion reactions, headaches (both ERT and migalastat) and antibodies)* 3. *Including disutilities for all attributes surveyed (mode of administration, infusion reactions, headaches (both ERT and migalastat) and antibodies) derived from the full surveyed population (not specifically excluding the 53 people that failed the response check)*
10	Equivalent ERT market share	Assumes that each ERT has a 50% market share

CEFD: clinically evident Fabry disease

Table 41 Results of company scenario analysis varying ERT price discount (CS Table D12.33)

Scenario	Incremental costs (£)	Difference in incremental costs (£)	% difference in incremental costs
Base case (3% discount)	1,268,674	-	
0% discount	1,188,848	−79,826	−6%
5% discount	1,321,891	53,217	4%
7% discount	1,375,108	106,434	8%

Most analyses had negligible impacts on incremental costs and QALYs. The improved efficacy analysis has assumptions which are based on insufficient evidence. The ERG believes that this analysis should be considered illustrative only. Furthermore, several analyses expose limitations of the utility and disutility estimates (section 4.3.64.3.6)

Table 42 Results of company scenario analyses (CS Table D12.34) (3% ERT price discount assumed)

	Incremental costs (£)	Difference in incremental costs (£)	Incremental QALYs	Difference in incremental QALYs
Base case	1,268,674	-	0.98	-
Utilities scenario 1: Miners et al. (2002)[53]	1,268,674	-	0.98	0%
Utilities scenario 2: Gold et al. (2002)[52]	1,268,674	-	0.98	0%
Reduced efficacy of ERT due to antibodies	1,268,912	0%	0.98	0%
Mean age of starting cohort 16 years	1,838,690	45%	1.28	31%
Average patient weight from ATTRACT	1,399,005	10%	0.98	-
Societal perspective	1,250,543	−1%	0.98	-
Improved efficacy of migalastat over ERT to reflect results on composite endpoint observed in ATTRACT	1,329,661	5%	1.23	26%
Time horizon 20 years	818,217	−36%	0.68	−30%
DCE disutility: full surveyed population	1,268,674	-	0.96	−2%
DCE disutility: all attributes	1,268,674	-	2.23	129%
DCE disutility: full surveyed population and all attributes	1,268,674	-	2.08	113%
Equal market share of ERTs	1,308,712	3%	0.98	0%

DCE: discrete choice experiment

4.3.9.3 Probabilistic Sensitivity Analysis

The company undertook a probabilistic sensitivity analysis that included all relevant model parameters. Costs for migalastat, frequency of ERT administration, and background mortality were omitted from the PSA as the values for these are fixed, and therefore not relevant for inclusion in a PSA. The PSA is run through a visual basic macro and takes approximately one minute to run 1000 simulations. The distributions used for classes of variables are reported in Table 43 (CS Table 12.25, page 209). The PSA macro code was appropriate, and correct.

Distributions chosen for the variables appear reasonable. Some distributions were assumed based on 20% variation from the mean.

Table 43 Distributions used in the company PSA

Variable	Distribution	Distribution parameters
Transition probabilities	Beta	95% CI from source
Discontinuation	Beta	95% CI upper and lower limits assumed to be +/- 20% of the mean
Adverse event probabilities	Beta	95% CI upper and lower limits assumed to be +/- 20% of the mean
Costs (acute event, follow-up, adverse event, healthcare contacts, ERT acquisition costs, ERT administration costs)	Lognormal	95% CI upper and lower limits assumed to be +/- 20% of the mean
Health state utilities	Beta	95% CI from source
Infusion disutility	Beta	95% CI from source
Adverse event disutility	Beta	95% CI from source (except influenza, for which 95% CI upper and lower limits assumed to be +/- 20% of the mean)
Duration of adverse event	Lognormal	95% CI upper and lower limits assumed to be +/- 20% of the mean
Productivity loss (patient and carer)	Lognormal	95% CI upper and lower limits assumed to be +/- 20% of the mean

The results of the company's probabilistic sensitivity analysis are reported in Table 44. The PSA results for costs and consequences are similar when compared to the company's deterministic base case analysis. Given that the analysis is a cost-consequence analysis, the probabilistic analysis provides no guidance for the robustness of any decision-making.

Table 44 Results of the company's probabilistic sensitivity analysis (CS Table D12.35) (3% ERT price discount assumed)

	Migalastat	ERT	Increment
Costs			
Average	£4,007,395	£2,776,990	£1,230,405
Lower bound (2.5th percentile)	£3,667,626	£2,490,194	£1,177,433
Upper bound (97.5th percentile)	£4,205,816	£3,029,639	£1,176,177
QALYs			
Average	14.34	13.36	0.98
Lower bound (2.5th percentile)	12.97	12.05	0.93
Upper bound (97.5th percentile)	15.48	14.49	0.99
LYs			
Average	19.06	19.06	0.00
Lower bound (2.5th percentile)	17.48	17.48	0.00
Upper bound (97.5th percentile)	20.02	20.03	-0.01

LYs: life years

4.4 Additional work undertaken by the ERG

In the company's base case analysis and all subsequent sensitivity analyses in their submission a price discount of 3% was assumed for both agalsidase alfa and agalsidase beta. In the analyses presented here, this assumed discount has been removed, with all costs assessed at list price. A separate confidential appendix has been prepared that reports the results of the ERG analyses with the confidential price for each ERT therapy from the Commercial Medicines Unit (CMU).

4.4.1 Scenario analysis methods

This section reports scenario analyses we conducted to address errors and flaws, and to further examine uncertainty in the company model. We conducted ten scenario analyses (Table 45). Nine of these examined a single issue. The tenth ERG scenario analysis is the ERG base case analysis. In addition to these analyses, threshold analyses were undertaken. More detailed methods and justification for these analyses are provided after the table.

Table 45 List of ERG scenario analyses

Analysis (#)	Description	Justification
0	Company base case (with ERT at list price)	Current NICE methods specify base case analyses should be at list price.
1	ERG Population: the starting proportions for cardiac complications and stroke were derived from the Fabry Registry.[46] Starting age 40 years.	The Fabry Registry[46] indicated that patients developed rates of cardiac and stroke events similar to those in ATTRACT by approximately the age of 40 (section 4.3.84.3.8).
2	Background mortality was derived from ONS Life Tables (2012-14)[11]	Background mortality did not match ONS reported rates resulting in overestimation of life expectancy (section 4.3.84.3.8).
3	Patient body weight was derived from the ATTRACT trial[20]	All RCTs that evaluated ERT had patient populations that weighed less than the general population.
4	Calibration of transition probabilities in the model to produce a life expectancy of 66.5 years (mean expected life expectancy with 50% male/female)[10]	The company model overestimates survival in Fabry patients (section 4.3.94.3.9).
5	Migalastat was assumed to have equivalent discontinuation to ERT	A clinical expert informed us that some patients would discontinue migalastat. We assumed the same very small discontinuation as ERT.
6	Migalastat patients who develop ESRD discontinue and move to untreated status	Migalastat SmPC does not recommend treatment in patients with ESRD.
7	Health state utilities for complications (ESRD, cardiac complications, stroke) have been derived from alternative sources	Health state utilities were higher than the ERG would expect (section 4.3.64.3.6).
8	The disutility for infusions was reduced by 50%.	The disutility for infusions appears to be inconsistent with EQ-5D and a credible theory of quality of life on dialysis (section 4.3.64.3.6).
9	The disutility for infusions was reduced by 75%.	As above.
10	ERG base case	This analysis provides pairwise comparisons to combined ERT and each ERT individually, but with ERG assumptions from analyses 1-8.

ESRD: end-stage renal disease; ONS: Office for National Statistics; SmPC: summary of product characteristics

Analysis 1: Alternative population

In analysis 1 we substituted values for the proportion of patients starting in each health state from the Fabry registry study by Eng and colleagues.[46] Values from the Fabry registry were reweighted to exclude patients with ESRD. Additionally, patients in the Fabry registry who experienced cardiovascular and stroke events had these events earlier than age 48 years. For cardiovascular events, the mean age was 39 years for males and 47.6 years for females. For stroke, the mean age was 38.6 years for males and 43.2 years for females. We started the model at age 40 years to take into account these event ages. Given that patients are diagnosed between a median age of 23 years in males and a median age of 32 years in females, according to the Fabry Registry,[46] we believe that the addition of eight years to the model time horizon is reasonable and may actually be a more plausible population given that patients will be eligible to take migalastat from age 16. The assumption of 50% females in the population from the company base case was maintained, as Fabry Registry data indicated that 50.1% of 2848 patients were female.[10] Table 46 below gives the values used in the company submission for starting states and the values used in the ERG's Analysis 1.

Table 46 Starting health states used in ERG scenario Analysis 1

Start State	ATTRACT (Company Base Case)	ERG Population[46]
% with pain, no other CEFD	14.0%	15.3%
% with CEFD	63.2%	60.0%
% with cardiac complications	21.1%	18.1%
% with ESRD	0.0%	0.0%
% with stroke	1.8%	6.7%

CEFD: clinically evident Fabry disease; ESRD: end-stage renal disease

Analysis 2: Corrected background mortality

Analysis 2 corrects erroneous background mortality data in the company submission model. The company model indicates that it uses life table data from ONS; however, the mortality rates in the model were slightly more than half the expected general population mortality rates after the 30th model cycle. According to the general population in ONS life tables for 2012-14, males would be expected to survive for 79.3 years and females 83.0 years,[11] whereas life expectancy in the company model is 83.4 years.

Analysis 3: Patient body weight from ATTRACT

As explained in section 4.3.34.3.3, the study population of four RCTs that evaluated ERT for Fabry disease all had populations with body weight significantly less than the general population at the same age. We therefore consider the ATTRACT patient population's mean weight to be more representative of Fabry disease patients.

Analysis 4: Model calibrated to produce estimated life expectancy from the Fabry Registry[10]

Analysis 3 seeks to reduce the overestimates of survival in the company model. Given the progressive nature of the disease, transition probabilities should increase over time, but we could not identify better time-dependent transition probabilities. Without better estimates, we created a multiplier variable in the model to increase transition probabilities with the following exceptions: background mortality and transitions from states with two or more complications to any other state. We calibrated the value of the multiplier to make the modelled life-expectancy equal to 66.5 years, which is the estimated survival in Fabry disease if a 50% female population is assumed for the Fabry Registry.[10] The calibration and the multiplier used in this analysis is shown below in threshold analysis B.

Analysis 5: Patients discontinue migalastat at the same rate as ERT

In the company base case no patients discontinue migalastat treatment. A clinical expert consulted by the ERG did not find this assumption plausible. In place, Analysis 4 assumes that patients discontinue at the same low 0.05% per year rate as ERT patients.

Analysis 6: Patients discontinue migalastat when they develop ESRD

Analysis 5 assumes that once patients enter ESRD they discontinue treatment in the migalastat arm, since migalastat is not recommended for use in patients with ESRD (draft SmPC).

It is unclear whether patients who discontinue migalastat would switch treatment to ERT. In this scenario analysis we assumed that patients who discontinued migalastat treatment would not receive ERT treatment. We were unable to model migalastat patients switching to ERT, as this would require adding additional states to the model, a structural modification that was unfeasible in the time available. It is also unknown whether doctors would choose to start patients with ESRD on ERT.

Analysis 7: Alternative utility values used for ESRD, cardiac complications and stroke

The ERG did not find the base case utilities for ESRD, cardiac complications, and stroke convincing (see section 4.3.64.3.6 for full explanation). We identified more plausible values and used these in Analysis 6. The utility values for ESRD are derived from the Liem and colleagues meta-analysis,[58] and the utility values for cardiac complications and stroke are derived from the Fabry patient population in Miners and colleagues.[53]

Table 47 Alternative utility values used in ERG scenario Analysis 7

Health state	Utility score	Source
ESRD	0.560	Liem et al. 2008[58]
Cardiac complications	0.674	Miners et al. 2002[53]
Stroke	0.594	Miners et al. 2002[53]

Analyses 8 and 9: Reduced infusion-related disutility

Similar to Analysis 6, the ERG did not find the disutility from infusions to be convincing. The 0.054 disutility is three times the corresponding disutility for moving from CEFD to ESRD (with corresponding dialysis). We applied simple percentage reductions to test the effect on QALYs. Analysis 8 reduces infusion disutility by 50% and Analysis 9 reduces the infusion disutility by 75%. A reduction of 50% is used in the ERG base case analyses.

Analysis 10: ERG base case

The tenth ERG scenario analysis combines the first eight scenario analyses into an ERG base case analysis (Table 45). The ERG base case is presented as three pairwise comparisons to migalastat: a combined ERT comparator (70% agalsidase alfa and 30% agalsidase beta, i.e. the same as the company's model), agalsidase alfa alone, and agalsidase beta alone.

4.4.2 Threshold Analysis methods

We conducted two threshold analyses. Analysis A tests how many times higher migalastat's on-treatment transition probabilities would need to be in order to result in zero incremental QALYs. We produced this threshold analysis because the data on migalastat's efficacy compared to ERT are highly uncertain. This threshold analysis provides a representation of how much migalastat's efficacy would need to change to produce a result that makes migalastat inferior in costs and consequences (more expensive and producing no more QALYs). Analysis A was

conducted on the company base case (Analysis 0) and on the ERG base case (Analysis 10). Within this threshold analysis we also explored varying the reduction in disutility, for illustrative purposes.

Analysis B, which is based on the ERG's scenario Analysis 4 (mean life expectancy of 66.5 years) investigated the multiplier that would be necessary to calibrate the company base case (Analysis 0) and the ERG base case (Analysis 10) to have a life expectancy of 66.5 years. As the ERT pairwise comparisons only differ in treatment costs, the multipliers produced through the threshold analyses are the same for each pairwise comparison.

4.4.3 Scenario analysis results

Table 48 presents the results of scenario analyses 1-9. The pairwise comparisons for the ERG base case are presented separately (Table 49), as only the cost of the interventions varies.

For the company's base case using the list price for ERT, migalastat has an incremental cost of £1,188,848 compared to ERT (Table 48).

Analysis 1 (alternative starting population) extends the time horizon of the model, which has the effect of increasing both costs and QALYs. The magnitude of the change is 7.2% for incremental costs and 7.1% for incremental QALYs. Analysis 2 (corrected ONS background mortality) has the effect of decreasing incremental costs by 5.7% and incremental QALYs by 4.7%, as life expectancy is reduced from 83.4 to 80.0 years, which is closer to general population values, but still appears high for Fabry disease. Analysis 3 (ATTRACT trial patient body weight) results in a 17.5% increase in incremental costs. Analysis 4 (higher migalastat on-treatment transition probabilities) substantially decreases incremental costs (39.5%) and QALYs (35.5%). Analysis 5 (equivalent discontinuation rates) had little effect on incremental differences in costs and QALYs, decreasing incremental costs by 2.5% and incremental QALYs by 0.2%. Analysis 6 (migalastat patients discontinue upon developing ESRD) decreases incremental costs by 7.1% and incremental QALYs by 2.0%. Analysis 7 (alternative health state utilities) reduces incremental QALYs by 0.03%. A 50% reduction in disutility from ERT infusions in Analysis 8 results in a 49.8% reduction in incremental QALYs. Similarly, reducing disutility from ERT infusions by 75% would result in a 74.6% reduction in incremental QALYs. Most of the incremental difference in in QALYs is due to infusion related disutility.

Table 48 Results of ERG scenario analyses (list price)

		Costs (£)			QALYs		
#	Description	Migalastat	ERT	Incremental	Migalastat	ERT	Incremental
0	Base Case (ERT at list price)	4,024,050	2,835,202	1,188,848	14.33	13.36	0.98
1	ERG population (age 40, complicationf rom Eng et al. 2007)[46]	4,307,918	3,034,104	1,273,814	15.35	14.30	1.04
2	ONS England & Wales Mortality (2012-14)[11]	3,834,387	2,713,788	1,120,599	13.66	12.73	0.93
3	ATTRACT patient body weight[20]	4,024,050	2,700,840	1,323,210	14.33	13.36	0.98
4	66.5 year life expectancy (Waldek et al 2009)[10]	2,594,566	1,874,896	719,669	9.03	8.40	0.63
5	Equivalent dis-continuation	3,994,433	2,835,202	1,159,231	14.33	13.36	0.97
6	No migalastat with ESRD	3,940,047	2,835,202	1,104,845	14.31	13.36	0.96
7	ERG health state utilities	4,024,050	2,835,202	1,188,848	13.87	12.89	0.98
8	50% infusion disutility	4,024,050	2,835,202	1,188,848	14.33	13.84	0.49
9	25% infusion disutility	4,024,050	2,835,202	1,188,848	14.33	14.09	0.25

ERT: enzyme replacement therapy; ONS: Office for National Statistics

Table 49 Results of ERG base case pairwise comparisons (list price)

Comparator	Costs (£)	Incremental Costs (£)	Life Years	Incremental Life Years	QALYs	Incremental QALYs
Migalastat	3,086,992		15.37		11.00	
ERT (blended)	2,196,454	890,539	15.47	-0.10	10.66	0.34
Agalsidase beta	2,047,431	1,039,561	15.47	-0.10	10.66	0.34
Agalsidase alfa	2,260,321	826,672	15.47	-0.10	10.66	0.34

While each of Analyses 1 to 8 are included in the ERG base case, the largest effects on incremental costs and QALYs are due to scenarios 3, 4 and 8: using patient body weights from ATTRACT to determine ERT dosage; calibrating the model to have a mean life expectancy of 66.5 years; and reducing the disutility from infusions. In the ERG base case analyses using the list price (Table 49), migalastat has an incremental cost of £890,539 and an incremental QALY of 0.34 compared to ERT.

A reduction in the modelled total life years for patients receiving migalastat is a result of patients having higher untreated probabilities due to the ESRD related discontinuation in Analysis 5. If migalastat patients instead switched to ERT, life years and QALYs would increase, but in lower magnitude than the corresponding increase in treatment costs. We were unable to model switching migalastat to ERT as this would have required re-structuring the model with several added health states. Additionally, we were unable to confirm whether a patient with ESRD would be considered for starting treatment on ERT.

Due to data errors, implausibility of assumptions, and lack of validity of many of the key model parameters, we consider the ERG base case more plausible than the company base case. The ERG analyses improve the face validity of the model, but the main flaw of the model, lack of time-dependent transition probabilities (with the exception of background mortality), is not addressed by our analyses. Creating a set of transition probabilities would require more data than the clinical trials of migalastat and ERT therapies, or Rombach and colleagues[1] provide, and would ideally incorporate correlated transition probabilities. Given that most clinical trials that include ERT have recruited fewer than 100 patients each[65] and had relatively short follow-up, we consider the most plausible source for relevant data will be through assessing outcomes from Fabry registries.

4.4.4 Threshold analysis results

Table 50 shows the results of the threshold analyses. Analysis A shows that in the company's base case, on-treatment transition probabilities for migalastat would have to be 74.3% higher in order to cancel out the QALY gains from migalastat. When the less favourable assumptions of the ERG base case are applied, on-treatment transition probabilities for migalastat would only have to be 9.4% higher. If the disutility for infusions is reduced by 75% instead of the 50% reduction in the ERG base case, the transition probabilities for migalastat need only to be increased by 3.9%. Threshold analysis A implies that if life-expectancy and disutility from infusions are both reduced, then a negligible reduction in on treatment efficacy would remove any benefits from migalastat treatment.

Analysis B shows that in order to make overall model estimates in line with life expectancy estimates from registry data,[10] all transition probabilities (with the exception of those from 2 or more complications to any state and background mortality rates) must be 5.85 times higher in the company base case, and must be 3.43 times higher in the ERG base case.

Table 50 Results of ERG threshold analyses (list price)

	Threshold analysis	Company Base Case	ERG Base Case
A	Reduced migalastat efficacy (on treatment transition multiplier) required to eliminate QALY benefit of migalastat	1.743	1.094
B	Transition multiplier necessary to calibrate population to have 66.5 year life expectancy	5.848	3.431

4.5 Summary of uncertainties and issues

There is a high level of uncertainty in the company's analysis, particularly concerning their assumption of clinical equivalence, the appropriateness of the model transition probabilities, and the utility decrement used for infusions. The ERG considers that the ATTRACT trial was not sufficiently powered to demonstrate clinical equivalence between migalastat and ERT and furthermore the company's model does not use any clinical outcomes from the company's clinical trials so that the relevance of the ATTRACT trial data to the long term outcomes modelled is unclear.

The majority of transition probabilities between the model health states do not vary with age, which leads to an overestimation of the life expectancy of patients with Fabry disease. The ERG analyses demonstrate the potential effect of these uncertainties, but do not resolve them. We believe that the set of assumptions used in the ERG analyses are more plausible and more conservative as they produce estimates that are more consistent with Fabry Registry data[10] and assume more plausible disutilities for infusions. However, the ERG analyses are based on assumptions that, whilst informed by some empirical data, still represent the ERG's best estimates rather than empirical proof. There remain large limitations in the evidence provided.

5 COST TO THE NHS AND PSS

The CS includes an analysis of the estimated budget impact of migalastat for the NHS in England. The budget impact analysis uses the assumptions and parameter estimates described for the economic model, together with the estimated prevalence of Fabry disease and those eligible for treatment with migalastat. The budget impact model estimates the total costs for England for the period 2017 to 2021.

5.1 Size of the eligible population

The budget impact model uses the estimated prevalence from a report by the Northern Genetics Service in the North of England[66] which estimated prevalence to be 1 in 64,600 (0.002%) (Table 51~~Table 51~~). Of those with signs and/or symptoms of Fabry disease, the CS estimates 78.6% would be diagnosed as having Fabry disease based upon the numbers of Fabry patients enrolled in the Fabry Disease Registry[67] and the Fabry Outcome Survey.[68] (N.B. The ERG does not have access to these databases to verify the estimates given). The CS assumes that 10% of patients are enrolled in both registries. The CS also assumes there is a further 3% of these patients who are diagnosed but not enrolled in the database.

Table 51 Derivation of the number of patients in England eligible for migalastat (CS Table D12.1)

Population of England (2016)	**55,218,701**
Prevalence of Fabry disease with signs/symptoms	0.002%
Number of patients with signs/symptoms of Fabry disease	**855**
Proportion of patients diagnosed with signs/symptoms	78.6%
Proportion of diagnosed patients receiving treatment	60%
Number of diagnosed, treated patients	**403**
Proportion of treated patients with amenable mutations	40%
Proportion of treated patients aged 16+	97%
Proportion of treated patients without ESRD	91%
Number of diagnosed treated patients eligible for migalastat	**142**

The CS assumes that 60% of diagnosed patients with signs and symptoms are being treated with ERT in the UK, based on the Fabry Disease Registry, and thus this proportion would apply to migalastat (the company assumes that migalastat is expected to be used in line with the starting and cessation criteria for ERT, although the ERG notes that patients with ESRD would not be eligible to continue to receive migalastat, whereas patients with ESRD could continue to receive ERT). The ERG suggests that 60% may be an underestimate as migalastat is an oral therapy and therefore potentially a greater number of patients may accept treatment than with the infusion-based ERT (the ERG explored this in sensitivity analyses, reported in section 5.45.4 below).

Migalastat is licensed for use in patients aged 16 years or over with Fabry disease with amenable mutations but who do not have ESRD. The CS assumes that 40% of patients have amenable mutations,[69-71] 97% of treated patients are aged 16 years or over,[72] and 91% of treated patients do not have ESRD.[73] Table 51Table 51 shows that the number patients who are eligible for migalastat in England using the derivation described is 142. The number in subsequent years is projected to increase in line with increases in the general England population to 148 by 2021. Thus, there is one additional incident treated patient each year (the ERG varies this in sensitivity analyses – see section 5.45.4 below).

5.2 Market share of the intervention and comparators

The future market share of migalastat was estimated by the company, based on previous market research studies and anticipated uptake of migalastat in the market. The CS uses different market share distributions for the incident and prevalent treated patients.
The CS assumes that the proportion of prevalent patients who switch to migalastat will gradually increase over time. In the same way, the proportion of incident patients who start on migalastat increases over time. The CS assumes that for patients receiving ERT the current proportion of patients receiving agalsidase alfa and agalsidase beta remains unchanged at 70% and 30% respectively. The market shares for patients treated with migalastat and ERT are shown in Table 52~~Table 52~~.

Table 52 Market shares in eligible patient population for migalastat (CS Table D13.3)

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3 Base case budget impact

The company's base case budget impact is shown in Table 53~~Table 53~~ (CS Table D13.6). The CS assumes an ERT discount rate of 3% and an average body weight of Fabry disease patients of 77.6 kg. The ERG also presents the budget impact using the ERT list price (Table 54~~Table 54~~).

The base case results suggest that the introduction of migalastat will lead to a substantial increase in acquisition costs and this is partly offset by savings to be made through the avoidance of ERT infusions. The CS budget impact analysis estimates that the increased annual cost of introducing migalastat could be [redacted] for England by year 5, i.e. [redacted] per patient per year.

Table 53 Base case budget impact disaggregated by cost categories (ERT price discount 3%) (CS Table D13.6)

	Year	Current market	Revised market	Difference
Acquisition costs	1	£19,125,699	[redacted]	[redacted]
	2	£19,269,568	[redacted]	[redacted]
	3	£19,413,436	[redacted]	[redacted]
	4	£19,557,305	[redacted]	[redacted]
	5	£19,701,173	[redacted]	[redacted]
Administration costs	1	£1,075,017	[redacted]	[redacted]
	2	£1,083,104	[redacted]	[redacted]
	3	£1,091,190	[redacted]	[redacted]
	4	£1,099,277	[redacted]	[redacted]
	5	£1,107,363	[redacted]	[redacted]
Total costs	1	£20,200,717	[redacted]	[redacted]
	2	£20,352,672	[redacted]	[redacted]
	3	£20,504,627	[redacted]	[redacted]
	4	£20,656,582	[redacted]	[redacted]
	5	£20,808,537	[redacted]	[redacted]

Table 54 Base case budget impact disaggregated by cost categories (ERT list price)

	Year	Current market	Revised market	Difference
Acquisition costs	1	£19,717,216	[redacted]	[redacted]
	2	£19,865,534	[redacted]	[redacted]
	3	£20,013,852	[redacted]	[redacted]
	4	£20,162,170	[redacted]	[redacted]
	5	£20,310,488	[redacted]	[redacted]
Administration costs	1	£1,075,017	[redacted]	[redacted]
	2	£1,083,104	[redacted]	[redacted]
	3	£1,091,190	[redacted]	[redacted]
	4	£1,099,277	[redacted]	[redacted]
	5	£1,107,363	[redacted]	[redacted]
Total costs	1	£20,792,233	[redacted]	[redacted]
	2	£20,948,638	[redacted]	[redacted]
	3	£21,105,042	[redacted]	[redacted]
	4	£21,261,447	[redacted]	[redacted]
	5	£21,417,851	[redacted]	[redacted]

5.4 Company and ERG sensitivity analyses

The CS has explored the effect on the budget impact results of changing: the discount price reduction for ERT; mean body weight; ERT market share; and the proportion of patients who have an amenable mutation. The results of the sensitivity analyses are shown in Table 55~~Table 55~~ (CS Table D13.8). Changes to the proportion of patients who have an amenable mutation had the greatest impact on the model results.

Table 55 Company sensitivity analysis on budget impact (ERT price discount 3%); Increase in annual total costs (CS Table D13.8)

Analysis	Year 1	Year 2	Year 3	Year 4	Year 5
Base case (3% price discount ERT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean body weight from ATTRACT rather than general population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume 30% of patients have amenable mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume 50% of patients have amenable mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume equal market share between agalsidase beta and agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG ran the sensitivity analyses with the ERT list price (Table 56~~Table 56~~). In addition, we investigated changes to assumptions and estimates where there is potential uncertainty: the prevalence of Fabry disease; the proportion of patients diagnosed with signs / symptoms; and the proportion of diagnosed patients receiving treatment. The ranges chosen are illustrative as we have not been able to identify any alternative plausible values for these parameters.

Table 56 ERG sensitivity analysis on budget impact (ERT list price); Increase in annual total costs

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Base case, List price ERT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7% price discount ERT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean body weight from ATTRACT rather than general population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume 30% of patients have amenable mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume 50% of patients have amenable mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume equal market share between agalsidase beta and agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalence of Fabry disease, 10% increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalence of Fabry, 10% decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients diagnosed, 85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients diagnosed, 70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients receiving treatment, 70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients receiving treatment, 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence treated patients, 50% higher	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG budget impact sensitivity analyses show that the estimated annual total additional cost of treating those Fabry patients who are eligible for migalastat would increase by between [redacted] by year 5. The analyses are most sensitive to the proportion of patients who have amenable mutations, the prevalence of Fabry disease, and the proportion of patients receiving treatment.

6 IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON DELIVERY OF THE SPECIALISED SERVICE

The CS provides a brief description of the impact of migalastat beyond direct health benefits (CS section E; section 14).

Literature is cited which describes the impact of Fabry disease on a patient's social interactions, school attendance, sport and leisure activities and ability to work. The literature selected shows an apparent increase in patients' ability to work since the introduction of ERT. It is implied that migalastat might enable patients to remain in employment for longer. Data from the Fabry Infusion Survey and the UK Fabry Disease Patient Survey are cited showing the disruption to employment caused by having ERT infusions. Therefore, it is proposed that an oral therapy such as migalastat would improve patients' ability to work, and minimise disruption to the working day.

The impact of migalastat for other government bodies is briefly discussed, but with no attempt at quantification. The CS asserts that any savings would not be anticipated to be different from those incurred through current therapy.

There is a brief discussion of costs borne by patients and their caregivers, and on the time spent by family members on providing care. In terms of the latter there is little quantification of time spent providing care. The CS suggests that the greatest requirement for care would be for Fabry patients experiencing renal failure, and a Spanish study of caregivers of chronic dialysis patients (non-Fabry disease) is cited. The company also suggests that carers are required to supervise infusions and time would be saved by use of an oral therapy [redacted].

(NB. The CS states that 50% of patients would require a nurse to deliver infusions, while the

remaining 50% of patients would self-administer or have infusions given by an informal caregiver (CS page 152). Therefore, carer time savings would only be realised in up to 50% of patients). Expert clinical advice to the ERG is that informal care requirements are minimal (e.g. help might be required to insert the needle, but little assistance is required thereafter). The MPS Society submission for this appraisal mentions that some patients have reported losing a day's pay fortnightly whilst on ERT.

7 CONSULTEE SUBMISSIONS

7.1 Patient and carer perspective

One consultee submission was received, from the MPS Society. The commentary in the submission on Fabry disease and its treatment (including migalastat) is based on informal feedback from clinicians and patients (it is noted that there are 10 patients that the Society knows of who are currently enrolled in a migalastat clinical trial), and on a survey of 174 Fabry patients (out of 357 Fabry patients on the MPS Society Registry =49% response) conducted by the Society examining patient treatment experiences. Limited details are given about the methodology of the survey and its results. In terms of the latter, some basic patient demographic details are given, followed by a series of selected quotes (some appear to be verbatim, but most are summarised), categorised into a group of patients who ceased treatment with agalsidase beta or who had their dose reduced during the agalsidase beta shortage (n=54); those who switched from agalsidase beta to agalsidase alfa during the shortage (n=44), and those who changed back to agalsidase beta at the end of the shortage (n=20). The limited data given suggests that (some) patients who had to withdraw from agalsidase beta treatment, or reduce their dose experienced an increase in symptoms (e.g. pain, fatigue, gastrointestinal problems) and events (e.g. TIA, strokes); and some patients who switched to agalsidase alfa experienced adverse effects and an increase in symptoms.

The MPS Society submission estimates that there are over 700 patients with Fabry disease, though it does not state if this is in England, or the UK.

7.2 Patient needs and experience

It is stated in the MPS Society consultee submission that MPS Society members welcome the prospect of having the choice of an oral rather than an infusion-delivered medicine. Not having to dedicate time every two weeks for an infusion is described as a 'huge relief' for patients.

At least three patients known to the Society who are currently enrolled in a migalastat clinical trial have verified that the treatment has given improvements in cardiac symptoms and stabilisation of kidney function (though it is not stated if this is in comparison to ERT or to no treatment). The submission mentions the benefits that patients have reported when switching from ERT to migalastat: improvements in mood and fewer mood swings; less fatigue and tiredness; less day to day impact (e.g. no longer having to store a pharmaceutical fridge; having to arrange cold store deliveries); and not having the inconvenience of taking a day each fortnight to receive an infusion (e.g. ability to plan longer holidays, not having to take time off work). Despite reporting these benefits, the submission also states that it is not in a position to judge the effectiveness and impact of side effects against existing ERTs.

The consultee submission reports that there is a sense of patient anxiety over the benefits of migalastat over ERT, and about making a treatment switch and a potential perceived loss of efficacy. The submission also highlights the potential issue of non-compliance to migalastat. The drug needs to be taken every other day, and at the same time of day, which might be difficult for some patients to adhere to (e.g. taking a tablet every other day might be harder to remember than taking a tablet every day). The ERG notes that the CS assumes equal compliance between migalastat and ERT, and that this is considered by the company to be a conservative assumption because it is expected that patients will be more compliant with an oral medicine than one administered by infusion (NB. compliance with study drug was [redacted] for migalastat and [redacted] for ERT in the ATTRACT trial). Given the issue of potential non-compliance highlighted by the MPS Society (also mentioned in the submission from Queen Elizabeth Hospital, Birmingham) the ERG questions whether the level of adherence reported in the trial would necessarily be achieved in practice, and whether the assumption of 100% compliance assumed in the CS economic model is realistic.

7.3 Health professional perspective

Consultee statements were received from the Royal Free London Hospital, and the Queen Elizabeth Hospital Birmingham (two of the five centres that treat adult patients).

The statements note that patient monitoring whilst on migalastat would be similar to ERT, with the same baseline and follow-up assessment of symptoms, cardiac and renal function and

neurology. Patients will still be required to visit one of the five adult centres twice a year if receiving migalastat. However, the requirement for fortnightly infusions will no longer apply, which would mean fewer nursing staff would be needed for home visits, or fewer hospital visits for those patients who have infusions there. There would also be a reduction in infusion reactions and immunogenicity.

The statement from the Queen Elizabeth Hospital Birmingham in particular raises the need to monitor compliance with migalastat. For example, patients may not see immediate benefits from taking the medication, and therefore may forget to take their tablets. It is noted that if patients are deteriorating this may be indicative of non-compliance or that the medication is not working for them. Counselling may therefore be required (this can be provided by medical, nursing and pharmacy staff). Whilst starting and stopping criteria are likely to be similar to those used in ERT (notwithstanding the prerequisite amenable mutation), these may need to be modified to take into account potential lack of benefit with migalastat in some patients.

The statements note that there is no need for additional technology or education for use of this medicine.

8 DISCUSSION

8.1 Summary of clinical effectiveness issues

The CS presents extensive results for a range of renal, cardiac, biochemical, HRQoL and safety outcomes from the ATTRACT and FACETS RCTs. However, of these, only adverse events in the ATTRACT trial directly inform the company's economic analysis.

The company cites GFR outcomes in ATTRACT in support of their assumption that migalastat and ERT are clinically 'comparable'. Due to uncertainty in the reported GFR results, the ERG does not agree that the ATTRACT trial provides unequivocal evidence of the equivalence of migalastat compared to ERT.

The population in the ATTRACT trial does not appear to be fully representative of patients with Fabry disease with mean age in their 40s and 50s; in particular, renal function was not suggestive of severe Fabry disease and patients with ESRD were excluded.

Baseline characteristics in the ATTRACT trial were unbalanced between the study arms, with the migalastat group having younger age, shorter time since diagnosis and lower 24-hour urine protein than the ERT group.

In both trials, the process used for randomising patients was unclear, primary analyses were not conducted on all randomised patients, and missing data were not accounted for in most analyses. These limitations put the trials' results at risk of selection and reporting biases.

Despite different aetiology, morbidity and prognosis of Fabry disease in males and females, results of planned subgroup analyses by male and female sex are not reported.

The FACETS trial is not directly relevant to the scope and is also limited by its short, 6-month, duration and concerns about the way statistical analyses were conducted differently for each outcome. Furthermore, the biochemical primary outcome is not used for decision making in clinical practice.

The CS presents additional evidence from OLE studies but these are limited by small sample sizes and lack of a comparator arm.

8.2 Summary of issues for costs and health effects

The model structure used in the cost consequence model appears to be largely consistent with the clinical pathway for patients with Fabry disease, however the model does not include a health state for patients with ESRD to have kidney transplants. The model reflects the disease progression of patients with Fabry to more severe health states of ESRD, cardiac symptoms, stroke and death. The model uses transition probabilities for disease progression, based upon the Dutch Fabry Cohort. Most transition probabilities are assumed to be constant over time which results in the model overestimating life expectancy for Fabry patients.

The model assumes that patients who develop ESRD continue to have migalastat treatment although the marketing authorisation does not allow this. The model assumes that no patients who have migalastat would discontinue treatment. The estimates chosen for utility values for some of the health states are inconsistent with those seen in other populations.

The model compares migalastat to a blended comparator of ERT (consisting of agalsidase alfa and agalsidase beta). The model assumes equivalence in the effectiveness estimates for migalastat compared to ERT. Therefore the life expectancy estimates for patients treated with migalastat and ERT are similar. The main difference in outcomes is due to disutility due to infusion. There is limited evidence from the company's clinical trial to support clinical equivalence.

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