NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Premeeting briefing

Migalastat for treating Fabry disease

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees, and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Evaluation Committee meeting and should be read with the full supporting documents for this evaluation.

Key issues for consideration

Nature of the condition

- Fabry disease is often treated with ERT, but the company notes a number of limitations of ERT (including the need for fortnightly infusions, infusion-related reactions and antibody formation).
  - What is the committee's view on of current patient need with availability of ERT?
  - What is the committee's understanding of the current use of ERT with regards to patient selection and dose titration?
  - Is this likely to change?
- The company proposes that migalastat may be offered when ERT would otherwise be considered, in patients with amenable mutations.
  - What is committee's view on the eligibility criteria for migalastat?
  - What is the committee's view on the proposed methods for identifying amenable mutations?

Impact of the new technology

- The ERG notes limitations in the ATTRACT trial (including insufficient power to demonstrate non-inferiority, exclusion of people with more-severe disease). The FACETS trial included an ERT-naive population, but the ERG notes that the comparator (placebo) is not directly relevant to the decision problem. Additional evidence was submitted from 2 open-label extension studies.
  - Does the committee believe that the clinical trials show short-term equivalence between ERT and migalastat?
  - Does this mean that long-term equivalence can be assumed?
- The company provides adverse event data from its trials, and also noted that ERT may be associated with infusion-related reactions and complications. What is the committee's view on the safety, tolerability and complications of migalastat compared with ERT?

Cost to the NHS and Personal Social Services and value for money

- The ERG noted a number of limitations and uncertainties in the company's cost–consequence model and assumptions. Do the committee believe that the general structure of the model is reliable?
  - The ERG stated that the disutility associated with infusions lacked face validity and the appropriateness of the discrete choice experiment was uncertain. What is the committee's view on the quality of life decrement associated with fortnightly infusions?
  - The company assumed 100% compliance and no discontinuation with migalastat. Does the committee consider this appropriate?
  - What is the committee's view on the assumed weight, starting distributions and mortality in the economic model?
- The company and ERG presented scenario analyses exploring alternative assumptions in the economic model. What is the committee's view on these?

Impact of the technology beyond direct health benefits

- Does the committee agree that replacing an infusion therapy with an oral one will allow patients more freedom from their disease treatments?

- What is the committee's view on the possible benefits of migalastat for patients and carers that are not captured in the evidence on health-related quality of life?
- What are the implications to the NHS of providing migalastat?
  - What are the implications of providing homecare arrangements for migalastat? This has not been considered in the company's submission but arrangements will be required to deliver migalastat from the highly specialist centres to patients.
  - Does the committee believe that there could be a reduced need for infusions and home nurse care for Fabry disease?

1 Nature of the condition

1.1 Fabry disease is an inherited disorder caused by mutations in the *GLA* gene which encodes the enzyme alpha-galactosidase A (α-gal A). Over 800 mutations of *GLA* that cause disease have been identified, with the majority causing misfolding of the enzyme which renders it non-functional or only partially functional. Decreased activity of α-gal A in lysosomes results in the accumulation of enzyme substrates (Gb3, and lyso-Gb3) which cause cellular damage in tissues throughout the body. Due to the location of *GLA* on the X chromosome, Fabry disease is generally more severe in men than in women. The manifestations of the disease can be classified as two main groups:

Classical Fabry disease

- Predominantly affects men but also some women
- Low or no residual α-gal A activity
- Usually early-onset
- Greater severity and shorter life expectancy than variant Fabry disease

Variant (non-classical Fabry disease)

- Predominantly affects women but also some men
- Some residual α-gal A activity, but this is often variable
- Usually later onset.

1.2 Fabry disease has many symptoms, which vary in age of onset, severity, and manner of progression. 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). Accumulation of Gb3 in lysosomes 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.

1.3 The prevalence of Fabry disease in England is approximately 0.002% meaning that there are 855 people with the disease. The company estimates that 142 people will be eligible for treatment with migalastat (see section 13 of the company submission). Highly specialist lysosomal storage disorder centres in England provide diagnosis, assessment and treatment for patients. Adult services are offered at Addenbrookes Hospital, University College London Hospital, Royal Free Hospital London, Salford Hope Hospital, and University Hospital Birmingham; children's services are provided at Birmingham Children's Hospital, Central Manchester Children's Hospital, and Great Ormond Street Hospital.

1.4 The life expectancy of people with Fabry disease has been estimated as 58.2 years for men and 75.4 years for women. In comparison with the general UK population, this would represent a reduction of life expectancy of approximately 21 years in men and 8 years in women.

1.5 Patient groups described how Fabry disease can have a profound impact on health-related quality of life:

- Symptoms of Fabry disease are often not recognised until adulthood, by which time significant organ system damage may have already occurred. Adults can experience kidney disease and failure, heart disease and stroke. Quality of life and life expectancy are reduced due to disease complications and people with Fabry disease may be

considered disabled. Some children may experience major complications of Fabry disease. People with Fabry disease may also be affected psychologically as it is a lifelong, multi-organ progressive disease.

- Due to the effects of Fabry disease, people may be unable to take part in normal activities leading to absences from education or work. Depending on the severity of symptoms, people with Fabry disease may require a carer at a relatively young age – often a close family member.

1.6 There is no cure for Fabry disease. The current options for the treatment of Fabry disease are bi-weekly infusions with one of 2 ERTs, agalsidase alfa and agalsidase beta, or supportive care to manage the symptoms and complications. The patient group notes that previous to the launch of ERT in 2001, people with Fabry disease only received palliative care, and that many people receiving ERT have demonstrated significant benefits and reductions in fatigue and gastrointestinal symptoms. Young adults with Fabry disease expect to have better disease outcomes than older generations as they have had access to ERT from a much earlier age. However, the company notes a number of disadvantages of ERT, including that it is a lifelong treatment that does not reverse the disease process or prevent adverse outcomes such as kidney failure and is less effective in patients who have already developed fibrosis. In addition, some people, most commonly men, may start to develop antibodies against the ERT, and the method of delivery of ERT carries a risk of infusion-related infection. The bi-weekly treatment schedule of ERT infusions is inconvenient, and if the person receives ERT infusions at home they must arrange for delivery and refrigerated storage of the medication. Despite the disadvantages of ERT, many people with

Fabry disease feel that the inconvenience of a bi-weekly infusion is a small price to pay for improved health. Patients note that a less-invasive oral therapy is an attractive option but it is important that it is at least clinically equivalent to ERT. The patient group also points out that compliance may be an issue for some people with Fabry disease particularly if they have mental health issues, for example, following a stroke.

2 The technology

2.1 Migalastat (Galafold, Amicus Therapeutics) is an oral, small molecule drug designed to designed to bind to the α-gal A enzyme as it is being made, helping it to fold correctly and improving its function (it acts as a 'pharmacological chaperone'). This aims to reduce the build-up of Gb3 and lyso-Gb3, and so reduce Fabry disease complications.

2.2 Migalastat has marketing authorisation in the UK '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'. The dosage recommended in the summary of product characteristics is 1 capsule of 150 mg of migalastat hydrochloride (equivalent to 123 mg migalastat) once every other day. Migalastat is not recommended in people with Fabry disease that have a glomerular filtration rate (GFR) <30ml/min/1.73m^2. Details of the licensed indication and relevant doses are available in the summary of product characteristics.

2.3 The company proposes that migalastat will be an alternative to ERT in people who are otherwise eligible for ERT and who have an 'amenable mutation'. This refers to the fact that migalastat is only expected to be effective in certain mutations of the *GLA* gene (those which cause misfolding and that can be addressed by

migalastat). Genetic testing of people with Fabry disease is performed during diagnosis and this information can be used to test amenability to migalastat. Standard genetic testing results can be compared against the Migalastat Amenability Table, which is published and updated on an ongoing basis by the company. Any mutations that are not listed can be sent to the company for testing at no cost to the NHS. Around 30–50% of people with Fabry disease are expected to have amenable mutations; the majority of these mutations are associated with the classic phenotype of Fabry disease.

2.4 Migalastat is indicated for use in people aged 16 years and older. ERT is indicated for use in people aged 8 years and older. Fabry disease is rarely diagnosed in children under 12 years of age unless there is an existing family history of the disease.

2.5 The summary of product characteristics states that headache is the most common (very common) adverse reaction for migalastat. Common adverse reactions include gastrointestinal disorders, skin rash, depression, palpitations, muscle spasms and proteinuria. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.6 The list price of migalastat is £16,153.85 per pack of 14 capsules (excluding VAT; company's evidence submission). The annual cost of treatment is £210,000 per patient (excluding VAT). The company has agreed a patient access scheme for migalastat. Details of the scheme were not available at the time of writing, but can be found in the company's patient access scheme submission document.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this evaluation was: to evaluate the benefits and costs of migalastat within its licensed indication for treating Fabry disease for national commissioning by NHS England.

3.2 Table 1 provides a summary of the company's decision problem, which was in line with the final NICE scope.

Table 1 Company's decision problem

Population	People with Fabry disease with a confirmed *GLA* mutation that is amenable to migalastat in vitro
Intervention	Migalastat
Comparators	• Agalsidase alfa • Agalsidase beta
Outcomes	• 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).

4 Impact of the new technology

The premeeting briefing only presents an overview of the results for studies including treatment with migalastat. For a more detailed presentation of the results, please see pages 72–133 of the company's submission.

Overview of the clinical trials

4.1 The company conducted a single overarching systematic literature review to identify studies of interest reporting clinical efficacy and safety, health-related quality of life (HRQoL) and economic evidence. The search identified 12 documents relevant to the clinical effectiveness of migalastat relating to 2 pivotal phase III randomised controlled trials (RCT):

- AT1001-011 ATTRACT (unpublished), 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).
- AT1001-012 FACETS (unpublished), a 6-month double-blind RCT, which randomised 67 treatment-naïve patients to receive migalastat (n=34) or placebo (n=33).
- AT1001-041 and AT1001-042 (ongoing), 2 phase III single-arm open-label extension (OLE) studies. Patients in these studies were recruited from both arms of ATTRACT and FACETS RCTs, and also from a phase II study, FAB-CL-205.

4.2 The company stated that the people enrolled in the studies were aged 16–74 years, had been diagnosed with Fabry disease and had a confirmed *GLA* mutation responsive to migalastat in vitro.

4.3 The final outcomes reported in ATTRACT and FACETS can be divided into renal function, cardiac function, HRQoL, and safety (see table 8 of the ERG report). 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. 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 but may not directly reflect patients' symptoms and do not themselves have a clear role in clinical decision making.

4.4 The company stated that ATTRACT was designed to show whether migalastat and ERT have comparable effectiveness. It noted that a standard non-inferiority analysis was not possible due to the small sample size, and therefore presented pre-specified criteria for comparability. Based on these criteria, migalastat would be considered comparable to ERT if 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, and the overlap in the 95% confidence intervals for these means was greater than 50%.

ERG comments

4.5 The ERG stated that no relevant studies were missed by the company's searches.

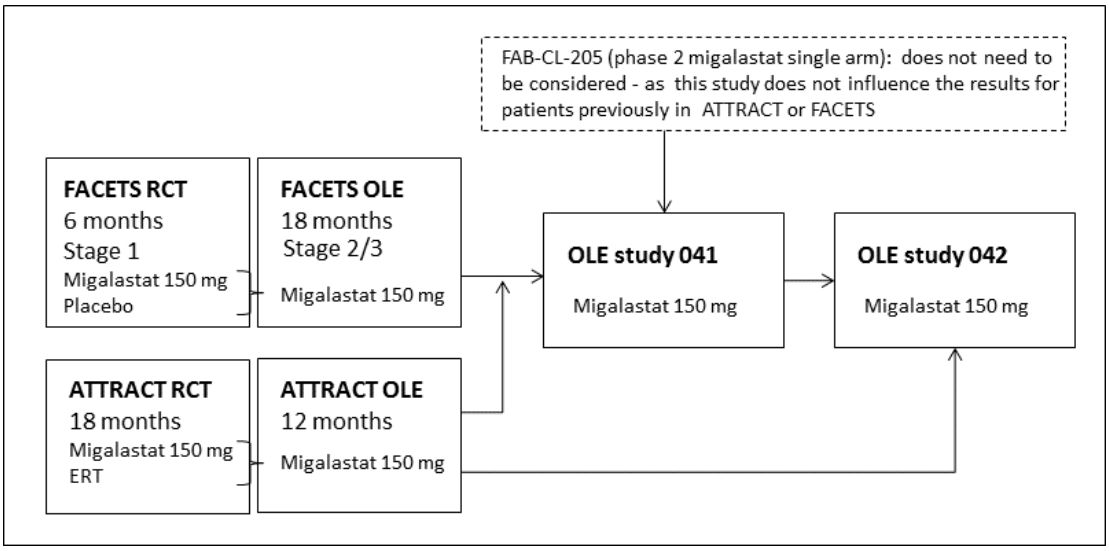
4.6 The ERG noted that the comparator for FACETS was placebo which is not a relevant comparator according to the decision problem. However, given the small evidence base for migalastat the ERG felt that it was appropriate to consider evidence from FACETS.

4.7 The ERG noted that the population of the ATTRACT trial excluded patients with end-stage renal disease (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 SPC, which states that migalastat is not recommended in patients with ESRD.

4.8 The ERG noted that the company was unclear which patients had entered the OLE studies. It appears that patients were recruited from both arms of both trials meaning that there is uncertainty over whether patients entering the OLEs has taken part in ATTRACT or FACETS.

4.9 The ERG stated that the studies providing clinical effectiveness evidence for migalastat are limited and that there are concerns relating to the trial design of both pivotal RCTs and the related OLE studies.

Figure 1 Summary of the relationship between ATTRACT, FACETS and OLE studies.



Source: ERG report, figure 5

Clinical study results

4.10 The trial population baseline characteristics for ATTRACT and FACETS are summarised in table 2. Both trials recruited more women than men. People in the ATTRACT trial had received prior ERT whereas most people in the FACETS trial had not.

Table 2 Summary of population baseline characteristics

Population baseline characteristics	ATTRACT		FACETS	
	migalastat (n=36)	ERT (n=21)	migalastat (n=34)	placebo (n=33)
Mean age (years)	50.2	46.3	40	45
Gender (% female)	56	57	65	64
Amenable mutations (%)	94	90	82	67
Years since diagnosis, mean±SE	10.2±2	13.4±2.6	5.7±1.2	7.1±1.4
Prior ERT (%)	100	100	15	36
Fabry phenotype (%) classic variant both unclassified	[redacted]	[redacted]	 64 4 4 29	 12 0 2 8
Fabry disease ≥2 organ systems (%)	[redacted]	[redacted]	17	29

Source: ERG report, table 4 and 6

Renal outcomes

4.11 The company 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. However, this does not apply to the [redacted] analysis of $eGFR_{CKD\text{-}EPI}$, since the difference in this outcome between the migalastat and ERT groups [redacted] the pre-specified 2.2 mL/min/1.73m^2. The direction of the difference in mean changes between trial arms [redacted] indicate that there is [redacted] for these outcomes.

4.12 For patients enrolled in the ATTRACT trial who continued treatment in the OLE study, 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 $eGFR_{CKD\text{-}EPI}$ was −1.7 mL/min/1.73 m^2 (95% CI −2.7, −0.8; n=31), both indicating a decline in kidney function.

4.13 In the FACETS trial, GFR changes are were measured over the 6-month trial duration. The company acknowledges that this 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 [redacted] for both the migalastat and placebo groups. In patients enrolled in the FACETS trial who continued treatment in the OLE study, the annualised changes in mGFR showed a decline; the eGFR results were inconsistent, although the confidence intervals (CI) included zero in all cases. Mean change in $eGFR_{CKD-EPI}$ over 0–36 months was [redacted] $mL/min/1.73m^2$ [redacted] 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. The ERG noted concern over the small patient numbers in this study, 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.

Cardiac outcomes

4.14 In ATTRACT, the change in left ventricular ejection fraction (LVEF) was measured over 18 months. There was a slight decrease in LVEF in the migalastat arm and slight increase in the ERT arm [redacted] but the changes from baseline and difference between the groups were less than 2% and the CIs for both groups include zero.

4.15 The company stated that, in the ATTRACT trial, left ventricular mass index (LVMI) showed a [redacted] and that in the ERT group the value at 18 months was not significantly

different from baseline (mean [95% CI] for migalastat versus ERT: -6.6 [-11, -2.2] versus -2 [−11, 7]). The ERG noted considerable uncertainty in these data as the number of patients included in this analysis is lower than specified in the modified intention to treat population with no reason given for the missing data. The company provided a breakdown of changes in LVMI according to gender and whether the patient had left ventricular hypertrophy (LVH) at baseline. The company stated that these data suggest that [redacted]

4.16 The company stated that LVPWT, IVSWT, and functional diastolic and systolic grade [redacted]

4.17 For patients from the ATTRACT trial who continued treatment in the OLE, the company presents 30-month data for baseline/post-baseline measures of LVMI in patients with amenable mutations (n=31). The mean annualised change from baseline in LVMI was −3.8 g/m^2 (95% CI −8.9, 1.3).

4.18 For patients from the FACETS trial continuing treatment in the OLE, LVMI changes were recorded at 18 and 24 months 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). Further measurements were made for a total of 30 or 36 months (mean LVMI change from baseline to 30/36 months [redacted] was [redacted] g/m^2 [redacted]

Composite clinical outcome

4.19 In the ATTRACT trial, a composite clinical outcome was used, comprising the rates of pre-specified renal, cardiac and cerebrovascular events and the rate of mortality, over 18 months.

4.20 During the 18-month treatment period in ATTRACT, 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.

Biochemical outcomes

4.21 In ATTRACT, changes in plasma lyso-Gb3 in the subgroups of patients with and without amenable mutations were measured. 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. For the outcome of α-Gal A activity in peripheral blood mononuclear cells the company states that normal α-Gal A activity is approximately 22 nmol/h/mg; [redacted] No biochemical outcomes were reported for patients in the OLE studies that had come from the ATTRACT trial.

4.22 For patients from the FACETS trial continuing treatment in the OLE, the activity of α-gal A in peripheral blood mononuclear cells [redacted] in males (no data

for females). The company stated that the reductions in plasma lyso-Gb3 that occurred during the FACETS trial 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.

Health related quality of life

4.23 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), and FACETS employed the Gastrointestinal Symptoms Rating Scale (GSRS).

4.24 For the ATTRACT trial the company reported SF-36 physical component summary mean score change over 0–18 months as shown in table 3. The company stated that SF-36 scores were comparable in the migalastat and ERT groups at baseline and there was little change in these scores over the 18-month study period and that the BPI pain severity component (where 10=maximum pain) indicates that patients experienced only mild pain at baseline, and this did not change over the 18-month treatment period.

4.25 The population numbers recorded for these health-related quality of life outcomes in ATTRACT do not match the expected modified intention to treat population (n=34 for migalastat and n=18 for ERT). 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 physical component score results in the ERT group).

Table 3 Health-related quality of life 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]

Source: ERG report, table 16

4.26 For patients from the FACETS trial continuing treatment in the OLE studies the company reported changes in scores for the same 5 GSRS domains. After 18 or 24 months of migalastat treatment patients had statistically significant improvement in the diarrhoea and indigestion domains compared with baseline. The company states that there was a trend for improvement in the reflux and constipation domains whilst symptoms of abdominal pain remained stable. For SF-36 the company only reports the vitality and general health domains (these were 4.0 (95% CI 0.1, 8.0) and 4.5 (95% CI 0.2, 8.9), respectively) and stated that the other domains were stable. The company also stated that BPI severity component scores did not change from baseline to month 24. It should be noted that only selected outcomes were been reported by the company, and no sample sizes are reported.

4.27 The patient group has heard from several members that have enrolled in the migalastat clinical trials. These people spoke favourably of the drug reporting fewer mood swings and a reduced impact on free time and work.

ERG comments

4.28 The ERG note that despite randomised group allocation, there were imbalances in patient baseline 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 company has used '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 ERG stated that 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.

4.29 The ERG stated that in the ATTRACT RCT, the company's ad hoc criteria for demonstrating comparability of migalastat and ERT were met for mGFR, but wide CIs indicated uncertainty. Results for eGFR were also reported but were inconsistent between 2 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 CIs 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.

4.30 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 CIs for both outcomes included zero change.

4.31 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.

4.32 Changes in biochemical outcomes reported in ATTRACT showed no clear pattern, except that activity of the target enzyme α-gal 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.

4.33 The ERG noted that there is uncertainty as to how long individual patients had received migalastat as it was not reported how many patients were recruited into the OLE from each arm of FACETS.

Adverse effects of treatment

4.34 The company provided adverse event data from ATTRACT, FACETS and the OLE studies following FACETS. 94–95% of patients in ATTRACT experienced a treatment emergent adverse event (TEAE), as did 91% of people in the FACETS trial. Nasopharyngitis and headache were the most common TEAE. Serious adverse events (SAE) were judged to be unrelated to migalastat therapy and no deaths have occurred.

4.35 The ERG stated that the adverse events data submitted by the company do not raise any safety concerns over the use of migalastat.

5 Cost to the NHS and personal social services and value for money

Model structure

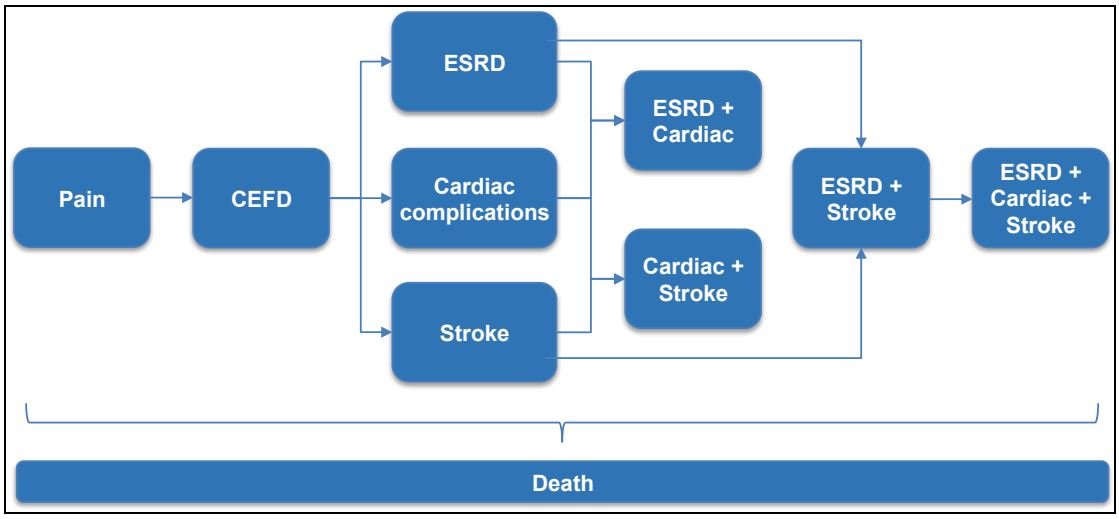
5.1 The company submitted a Markov state-transition model to estimate the costs and health effects of migalastat compared with ERT in people with Fabry disease. The health states in the model represent the progression of Fabry disease over time. All health states are divided into incident (acute events) 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.

5.2 The model structure is summarised in figure 2. Patients in the pain health state exhibit neuropathic pain and may progress to the clinically evident Fabry disease (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.

5.3 The model took the perspective of the NHS and Personal Social Services. It had a lifetime (48-year) time horizon, and a cycle length of 1 year. Costs and benefits were discounted at a rate of 3.5% per year.

Figure 2 Company model schematic



Source: Company submission, Figure D12.1

ERG comments

5.4 The ERG clarified that 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 ERG stated that 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.

Model inputs and assumptions

5.5 The model structure and the values for transition probabilities between disease states are based on a Dutch study done in a Fabry disease cohort. It is assumed that this is equivalent to a UK Fabry population. A number of structural assumptions were made in the company's version of this model:

- ERTs are equivalent and can be grouped as a 'blended comparator'.
- Migalastat is clinically equivalent to ERT.
- Patients receiving migalastat continue treatment until death, whilst patients receiving ERT discontinue treatment.
- Treatment adherence is 100%.
- Transition probabilities do not vary over time.
- Patients cannot develop two complications in one model cycle (one year).
- People with Fabry disease have a similar body weight to the UK general population.

5.6 The starting distribution of patients into the 5 health states was based on the baseline measurements of the ATTRACT trial population. The company stated that this population is representative of people with Fabry disease in England.

5.7 Drug costs consist of drug acquisition 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). Details of the agreed patient access scheme for migalastat were not available at the time of writing, but can be found in the company's patient access scheme submission document. The cost of ERT was taken from the BNF and the company states that ERT is available with a confidential discount and assumed this discount is 3%. The ERG has also prepared an analysis based on the true discount for ERT; details can be found in a confidential appendix to the ERG report. 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 down to the nearest vial and uses average population body mass values. The company has stated that it was advised by clinical experts that 50% of people receiving ERT self-administer and only require 1 nurse visit per year, whereas the other 50% will have their ERT administered by a nurse at home. Nurse visit costs were estimated at £91 per hour, based on Personal Social Services Research Unit (PSSRU) data. 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.

5.8 The company also provided estimates for costs associated with each health state. Health state costs included diagnostic, laboratory and imaging tests, primary and secondary care appointments, hospitalisations and treatment of complications. The costs were derived from NHS reference costs and PSSRU data (see table 33 of the ERG report). The frequency of diagnostic, laboratory and imaging tests for all patients with Fabry disease were taken from

the adult Fabry disease standard operating procedure, with the unit costs taken from the NHS reference costs.

5.9 The costs for treating adverse events were also considered for each specific adverse event. The costs ranged from £0.06 (headache) to £47.28 (influenza), and were sourced from the BNF and PSSRU (see table 34 of the ERG report).

5.10 The model captures HRQoL by assigning utility scores to each health state. The utility scores were taken from the Dutch study. Over the course of disease progression, HRQoL deteriorates as patients transition to worse health states with an increasing number of major complications. The effects of adverse event and infusions on quality of life were captured by applying utility decrements (disutilities). Infusion-related utility decrements were based on a discrete choice experiment (DCE) 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; the company stated that infusion-associated reactions and antibody formation may also affect quality of life, but disutilities for these were not included in the base case.

ERG comments

5.11 The ERG noted that in the model transition probabilities between disease states stay constant throughout the life of the patient. The ERG stated that this is implausible as 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. This leads to transition probabilities that are too low to be realistic. It is also not

possible for patients to move backwards between disease states, for example following a kidney transplant.

5.12 The company's model assumes that Fabry patients have similar body mass to the UK general population. In ATTRACT and other clinical trials conducted in Fabry disease the average patient body mass is less than that of people in the general population of the same age. In ATTRACT average body mass was 74.1 kg (males and females, 44% of the included population were male) and average age was 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. The ERG stated that it appears likely that the company base-case analysis overestimates the body weight of patients receiving ERT because the dose of ERT is based on body weight, this assumption would increase the cost of the comparator.

5.13 The ERG had concerns over the starting distribution across health states in the model. The starting distributions were based on baseline measurements from the ATTRACT trial. The ERG stated that this trial enrolled people with less severe manifestations of Fabry disease than those expected in clinical practice.

5.14 The ERG noted strong concerns about the mortality estimates used in the company's model. The ERG described that the company used background mortality rates from UK life tables, and Fabry disease-specific mortality rates from the Dutch study – whichever was higher. However, it appears that background mortality estimates used in the model are unrealistically low and did not match the data reported by the Office for National Statistics (2012–2014). 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 (83.4 years). Another strong concern is that the model uses disease-specific mortality rates whenever these were higher than the age-dependent background rates, but the disease-specific mortality rates did not vary with age. The ERG suggested that 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.

5.15 The ERG noted that the company had not allowed for poor compliance or discontinuation of migalastat treatment. Clinical advice to the ERG and submissions 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. Some patients may find it difficult to adhere to the every-other-day dosing, particularly if they have had a stroke. The ERG also noted that migalastat is not recommended for use in patients with ESRD and that people developing ESRD would discontinue treatment with migalastat. A scenario analysis was conducted by the ERG to address this (table 48 of the ERG report).

5.16 The ERG note that there is a lack of face validity in the utility 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), which seems unlikely. The disutilities for infusions have been collected using a DCE (in the general population) and it is unclear how comparable estimates from DCE are to those derived using the EQ-5D. In addition, the model assumes ESRD, cardiac complications and stroke all have the same utility value, despite there being large differences in the quality of life for these complications.

Company's results and sensitivity analysis of cost-consequence analysis

5.17 The results of the company's cost–consequence analysis are presented as costs, life-years, and quality-adjusted life years (QALYs). 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 4 Company base-case cost–consequence analysis results (assumed 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

Source: ERG report, table 35

Table 5 Company base-case costs (assumed ERT 3% price discount)

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

Source: ERG report, table 37

5.18 Results for deterministic one-way sensitivity analyses were reported as tornado diagrams. 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 notes 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 and emphasises the importance of disutilities for infusions, as these make up virtually all of the difference in QALYs between migalastat and ERT.

5.19 The company's probabilistic sensitivity analysis results for costs and consequences are similar when compared to the company's deterministic base case analysis. The ERG noted that, given that the analysis is a cost-consequence analysis, the probabilistic analysis provides no guidance for the robustness of any decision-making.

5.20 The company conducted scenario analyses in 10 categories: ERT price discounts, alternative utility scores, reduced ERT efficacy due to antibodies, age 16 at baseline, ATTRACT average body mass, societal perspective, greater migalastat effectiveness, 20-year time horizon, average infusion disutilities and equivalent ERT market share. When the effectiveness of migalastat was assumed to be greater than ERT (the company stated that this reflected results from the composite endpoint in ATTRACT), incremental costs associated with migalastat increased by 5% (to £1,329,661), and the incremental QALYs increased by 26% (to 1.23), compared with the company's base case.

5.21 The ERG emphasised that there is a high level of uncertainty in the company's analysis, particularly concerning the assumption of

clinical equivalence, the appropriateness of the model transition probabilities, and the utility decrement used for infusions. The ERG considered 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.

ERG exploratory analyses

5.22 The ERG conducted 10 scenario analyses to address flaws and examine the uncertainties in the model (table 6). The tenth ERG scenario analysis combines the first eight scenario analyses into an 'ERG preferred analysis'. The ERG preferred analysis is presented as three pairwise comparisons with 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.

Table 6 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. Starting age 40 years.	The Fabry Registry indicated that patients developed rates of cardiac and stroke events similar to those in ATTRACT by approximately the age of 40.
2	Background mortality was derived from ONS Life Tables (2012-14)	Background mortality did not match ONS reported rates resulting in overestimation of life.
3	Patient body mass was derived from the ATTRACT trial	All RCTs that evaluated ERT had patient populations that has less mass than the general population.
4	Calibration of transition probabilities in	The company model overestimates

	the model to produce a life expectancy of 66.5 years (mean expected life expectancy with 50% male/female)	survival in Fabry patients.
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.
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.
9	The disutility for infusions was reduced by 75%.	As above.
10	ERG preferred analysis	This analysis provides pairwise comparisons to combined ERT and each ERT individually, but with ERG assumptions from analyses 1-8.

Source: ERG report, table 45

5.23 In the ERG preferred analysis using the list price for ERT, migalastat has an incremental cost of £890,539 and an incremental QALY of 0.34 compared with ERT.

5.24 Analysis 3 (ATTRACT trial patient body mass) resulted in a 17.5% increase in incremental costs. Analysis 4 (higher migalastat on-treatment transition probabilities) substantially decreased incremental costs (39.5%) and QALYs (35.5%). Analysis 8 resulted in a 49.8% reduction in incremental QALYs.

5.25 The ERG was unable to model switching migalastat to ERT as this would have required re-structuring the model with several added health states. The ERG was also unable to confirm whether a

patient with ESRD would be considered for starting treatment on ERT.

5.26 The ERG considered that its 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 the new analyses. Creating a set of transition probabilities would require more data than the clinical trials provide, and would ideally incorporate correlated transition probabilities. Given that most clinical trials that include ERT have recruited fewer than 100 patients each and had relatively short follow-up, the ERG consider the most plausible source for relevant data will be through assessing outcomes from Fabry registries.

5.27 The ERG noted that the majority of transition probabilities between the model health states in the company's model do not vary with age, which lead to an overestimation of the life expectancy of patients with Fabry disease. The ERG stated that its analyses demonstrate the potential effect of these uncertainties, but do not resolve them. The set of assumptions used in the ERG analyses are more conservative as they produce estimates that are more consistent with Fabry Registry data 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. The ERG stated that there remain limitations in the evidence.

Budget impact analysis

5.28 The company presented a budget impact analysis based on 142 people with Fabry disease in the UK. This population is a proportion of the total number of people assumed to be receiving treatment for Fabry disease in the UK. It is assumed that 40% of

these people will have amenable mutations for migalastat treatment. The number of people eligible for migalastat is predicted to increase by one person per year. An average body mass of 77.6 kg was used to calculate the required ERT doses. The company's budget impact analysis is reported in tables 7 and 8.

5.29 ERG sensitivity analyses showed that these calculations are most sensitive to the proportion of patients who have amenable mutations, the prevalence of Fabry disease, and the proportion of patients receiving treatment.

Table 7 Company's estimate of the number of people eligible for treatment with migalastat

Population of England in 2016		55,218,701
Prevalence of Fabry disease with signs/symptoms	0.002%	855
Proportion of patients diagnosed with signs/symptoms	78.6%	672
Proportion of diagnosed patients receiving treatment	60%	403
Proportion of treated patients with amenable mutations	40%	161
Proportion of treated patients aged 16+	97%	156
Proportion of treated patients without ESRD	91%	142
Number of diagnosed patients eligible for migalastat		142

Table 8 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]

Source: ERG report, table 54

6 Impact of the technology beyond direct health benefits and on the delivery of the specialised service

6.1 The company states that it does not anticipate that any extra infrastructure or any change to the way services are delivered will be required if people with Fabry disease are treated with migalastat instead of ERT. There will be a reduction in the need for infusion deliveries, homecare nurses and infusion clinic appointments. However, arrangements for the delivery of migalastat to patients will need to be made by the highly specialist centres. Genetic testing is performed as standard to diagnose Fabry disease; the results of this are used to determine if the mutation is amenable to migalastat. Any additional testing needed to identify whether new mutations are amenable to migalastat will be at the expense of the company.

6.2 The company provided a brief description of the impact of migalastat beyond its direct health benefits. It is explained that patient ability to work has increased since the introduction of ERT. 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.

6.3 The company suggests that carers are required to supervise infusions and time would be saved by use of an oral therapy [redacted]

[redacted] The company stated 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. Therefore, carer time savings would only be realised in up to 50% of patients. Expert clinical advice stated that informal care requirements are minimal (e.g. help might be required to insert the needle, but little assistance is required thereafter). The patient group noted that some patients have reported losing a day's pay fortnightly whilst on ERT.

7 Equalities issues

7.1 No equality issues were raised during the scoping consultation and workshop, or were identified in the evidence submissions NICE received from the company and experts (clinical and patient).

8 Innovation

8.1 The company highlighted that migalastat is the first oral disease-modifying treatment for Fabry disease and therefore fills an unmet clinical need. The company claims that switching to an oral therapy from an infusion therapy increases patient choice, reduces pressure on homecare and infusion services and offers greater patient convenience. Migalastat also avoids the risk of infusion-associated reactions and infections, removes the need for pre-infusion medication, avoids the immune response associated with ERT, has broader tissue distribution and more closely mimics natural enzyme trafficking than bi-weekly infusions.

8.2 The patient group state that if migalastat is as effective as ERT then it will be a huge relief for patients to not be inconvenienced by bi-weekly infusions. This has the potential to reduce the impact treatment has on work, holidays and social events.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance or NHS England Policy Documents

There is no related guidance for this technology.

Appendix B: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004059/WC500208434.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID868]

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of migalastat within its licensed indication for treating Fabry disease for national commissioning by NHS England.

Background

Fabry disease (also known as Anderson-Fabry disease) is an inherited lysosomal storage disorder caused by mutations in the GLA gene which encodes the enzyme alpha-galactosidase A. Mutations in the GLA gene change the enzyme's structure and function and prevent it from breaking down a fat called globotriaosylceramide (Gb3). Progressive accumulation of Gb3 in cells can lead to a wide range of symptoms which may not appear in everyone with the disease.[1]

The number and severity of symptoms varies between patients and can include short term severe pain or burning sensation, which starts at the extremities and spreads throughout the rest of the body (often referred to as a 'Fabry crisis'), gastrointestinal complications such as diarrhoea, nausea and abdominal pain, headaches, inability to sweat properly (hypohidrosis), vertigo and hearing impairment. Other body sites that can also be affected include the skin, eyes, kidneys, heart, brain and nervous system. Symptoms usually worsen as patients get older, except pain, which often improves after childhood.[2] Fabry disease can lead to heart and renal failure and can raise a patient's risk of stroke.

Fabry disease is X-linked, therefore men who have only one copy of the defective gene are more likely to develop the disease.[3] Men can have either:

- no alpha-galactosidase A activity, in which case symptoms will usually develop during childhood and be quite severe (this is the standard presentation); or
- some alpha-galactosidase A activity, in which case symptoms develop between the ages of 60 and 80 years (this is atypical and these men can remain asymptomatic for many years before being diagnosed with Fabry disease).[3]

Because women have two X chromosomes, enzyme activity is extremely variable due to random X-chromosomal activation. Therefore, some women will have no disease activity, while others may have mild, moderate or severe symptoms. It has been estimated that there are approximately 400 people in England with Fabry disease.[3]

There is currently no cure for Fabry disease. Enzyme replacement therapy (agalsidase alfa and agalsidase beta) are administered to replace the non-functioning enzyme[2] and help prevent the development of disease-related symptoms in younger patients, and slow disease progression in people with

more advanced disease.[4] For people with severe kidney disease, a kidney transplant may be considered. Fabry disease and related conditions (collectively termed lysosomal storage diseases) are usually managed in specialist centres in England.

The technology

Migalastat (Galafold, Amicus Therapeutics) is a molecule that binds with and refolds the faulty alpha-galactosidase A enzyme to restore its activity. This allows it to enter the lysosome and to break down Gb3. It is administered orally.

Migalastat does not currently have a marketing authorisation in the UK. It has been studied as monotherapy in clinical trials in people aged 16 years or older with Fabry disease who have a mutation in the GLA gene that is known to be responsive to migalastat in vitro, compared with placebo. Migalastat has been studied in people who have not received previous treatment, and in those who have previously received enzyme replacement therapy.

Intervention(s)	Migalastat
Population(s)	People with Fabry disease with a confirmed GLA mutation that is amenable to migalastat in vitro
Comparators	• Agalsidase alpha • Agalsidase beta
Outcomes	The outcome measures to be considered include: • 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).

Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Cost to the NHS and Personal Social Services (PSS), and Value for Money	• budget impact in the NHS and PSS, including patient access agreements (if applicable) • robustness of 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) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only

	in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. The availability of any nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit should be taken into account. If appropriate, the evaluation should include consideration of the costs and implications of additional testing for genetic mutations, but will not make recommendations on specific diagnostic tests.
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. http://www.england.nhs.uk/wpcontent/uploads/2013/06/e06-lyso-stor-dis-child.pdf NHS England Standard Contract for Metabolic Disorders (Adult), 2013. http://www.england.nhs.uk/wpcontent/uploads/2013/06/e06-metab-disordersadult.pdf Department of Health rare diseases strategy, November 2013. https://www.gov.uk/government/publications/rare-diseases-strategy

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID868]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Amicus Therapeutics (migalastat) Patient/carer groups • Genetic Alliance UK • MPS Society Professional groups • Addenbrooke's Lysosomal Disorders Unit • Department of Endocrinology, University Hospital Birmingham Foundation Trust • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Free Lysosomal storage disorders unit Others • Department of Health • NHS England	General • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland Comparator companies • Genzyme Therapeutics (agalsidase beta) • Shire Human Genetic Therapies (agalsidase alfa) Relevant research groups • MRC Clinical Trials Unit • National Institute for Health Research Associated Public Health Groups • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the evaluation; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the recommendations.

All non-company/sponsor consultees are invited to make an evidence submission or submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the recommendations.

Commentators

Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the final evaluation documentation for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary*)*.

All non-company/sponsor commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Migalastat (Galafold™) for the treatment of Fabry disease in patients with amenable mutations

10th March 2016

Contents

List of tables and figures

Glossary of terms

Term	Definition
Chaperone therapy	In lysosomal storage disorders unstable, unfolded or misfolded proteins may be eliminated or retained in the endoplasmic reticulum rather than being transported to the lysosome. Pharmacological chaperone therapy is an emerging approach to treat lysosomal storage diseases. Small-molecule chaperones interact with mutant enzymes, favour their correct conformation and enhance their stability and lysosomal trafficking. Once in the lysosome, the pharmacological chaperone disassociates and the enzyme is free to break down substrate. Chaperone therapy allows the body to use its own endogenous enzyme, rather than one that is artificially introduced.
Amenable mutation	A mutation that is responsive to chaperone therapy. In the context of this submission, amenability specifically refers to responsiveness to migalastat therapy.

List of abbreviations

α-Gal A	alpha-galactosidase A
ACC	American College of Cardiology
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AE	adverse event
AHA	American Heart Association
AIDS	acquired immunodeficiency syndrome
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AT1001	migalastat
AV	atrioventricular
BID	twice daily
BIM	budget impact model
BL	baseline
BLISS	Barisoni Lipid Inclusion Scoring System
BNF	British National Formulary
BPI	Brief Pain Inventory
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CBF	cerebral blood flow
CCB	calcium channel blocker
CEFD	clinically-evident Fabry disease
CHD	coronary heart disease
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CHQ	Child Health Questionnaire
CI	confidence interval
CKD	chronic kidney disease
CNS	central nervous system
CrCl	creatinine clearance
CYP450	cytochrome P450 enzyme system

DCE	discrete choice experiment
DNA	deoxyribonucleic acid
DSA	deterministic sensitivity analysis
E/A	early-to-late ventricular filling ratio
ECG	electrocardiogram
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
EMA	European Medicines Agency
ENT	ear, nose and throat
EQ-5D	European Quality of Life-5 Dimensions
EQ-VAS	European Quality of Life Visual Analog Scale
ERT	enzyme replacement therapy
ESRD	end-stage renal disease
EU	European Union
EuroQoL	European Quality of Life scale
FDA	Food and Drug Administration
FSIG	Fabry Support and Information Group
G-BA	Gemeinsame Bundesausschuss
GD	Gaucher disease
GFR	glomerular filtration rate
GI	gastrointestinal
GL1	glucosylceramide
GL3	globotriaosylceramide NOTE: this can also be abbreviated as GB3 but has been referred to as GL3 throughout this submission
GLA	gene for alpha galactosidase A
GLP	good laboratory practice
GP	general practitioner
GSRS	Gastrointestinal Symptom Rating Scale
GVUS	genetic variations of uncertain significance
H_2	histamine type 2
HCl	hydrochloride
HCM	Hypertrophic cardiomyopathy
HDL-C	High-density lipoprotein cholesterol
HEK	human embryonic kidney
HF	heart failure
HPLC	high performance liquid chromatography
HR	hazard ratio
HRQL	health-related quality of life
HTA	health technology assessment
IAR	infusion-associated reaction
IC	interstitial capillary
ICD	implantable cardioverter defibrillator
ICER	incremental cost effectiveness ratio
Ig	immunoglobulin
ITT	intent-to-treat
IV	intravenous
KDIGO	Kidney Disease/Improving Global Outcomes
LA	left atrium
LBBB	Left bundle branch block
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LSD	lysosomal storage disease
LSM	least square mean
LV	left ventricular

LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMi	left ventricular mass index
lyso-Gb3	globotriaosylsphingosine
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
MFS	midwall fractional shortening
$mGFR_{iohexol}$	modified glomerular filtration rate - iohexol
MI	myocardial infarction
mITT	modified intent to treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
MWT	mean ventricular wall thickness
NA	not applicable
NCS	National Collaborative Study
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NO	nitric oxide
NR	not reported
NS	not significant
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OD	once daily
OLE	open-label extension
ONS	Office of National Statistics
PBMC	peripheral blood mononuclear cell
PCS	Physical Component Summary
PD	pharmacodynamics
PedsQL	Pediatric Quality of Life Inventory
PET	positron emission tomography
P-gp	P-glycoprotein
PK	pharmacokinetic
PLAX	parasternal long axis
PNS	peripheral nervous system
PRO	patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	personal social services
PTCA	percutaneous transluminal coronary angioplasty
PTSMA	percutaneous transluminal septal myocardial ablation
QALY	quality-adjusted life year
QOD	once every other day
RA	rheumatoid arthritis
rCBF	regional cerebral blood flow
RI	renin inhibitor
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SF-36	Short Form-36 Health Survey
SNHL	sensorineural hearing loss
SNRI	serotonin-norepinephrine reuptake inhibitor
SRI	serotonin reuptake inhibitor
SRT	substrate reduction therapy

SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TCD	transcranial Doppler
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
T_{max}	Time to maximum plasma concentration
UA	unstable angina
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
UTI	urinary tract infection
V_{O2}	oxygen consumption
VT	ventricular tachycardia
WBC	white blood cell
WML	white mass lesion
WTP	willingness to pay
YFEOD	years free of end-organ damage

Executive Summary

Migalastat

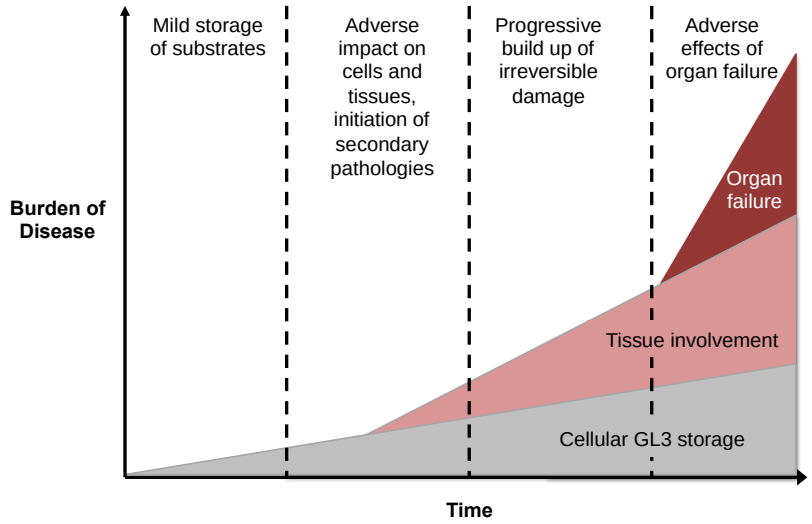
Migalastat (Galafold™) is a first-in-class, oral, innovative small molecule that provides personalised targeted chaperone therapy for patients with Fabry disease, a rare inherited metabolic condition. Migalastat is currently being assessed by the European Medicines Agency (EMA) for the long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease and who have an amenable mutation. Positive Committee for Medicinal Products for Human Use (CHMP) opinion is expected at the end of March 2016, with full marketing authorisation expected in May or June 2016. Migalastat is a long-term, chronic, therapy and will be available in a pack with 14 capsules at a list price of £16,153.85 per pack. The recommended dose is 1 capsule (123 mg) once every other day (Amicus Therapeutics, 2016c).

In Fabry disease, insufficient activity of the enzyme α-galactosidase A (α-Gal A) leads to the accumulation of globotriaosylceramide (GL3) and other products in the lysosomes of cells (Germain, 2010; El-Abassi et al., 2014). Migalastat is a pharmacological chaperone that is designed to selectively and reversibly bind with high affinity to the active sites of certain mutant forms of α-Gal A, the genotypes of which are referred to as amenable mutations. Migalastat binding stabilises these mutant forms of α-Gal A in the endoplasmic reticulum and facilitates their proper trafficking to lysosomes where dissociation of migalastat restores α-Gal A activity, leading to the catabolism of GL3 and related substrates for normal function (Amicus Therapeutics, 2016c)(Section 2.2).

Nature of the condition

In Fabry disease, the accumulation of GL3 and other products damages cells and leads to progressive and irreversible organ damage, typically involving the nervous system, endothelium, kidney, and heart, as well as other tissues (see Figure 1) (Germain, 2010; El-Abassi et al., 2014).

Figure 1: Schematic model of the progression of Fabry disease



GL3=globotriaosylceramide.
Source: Eng et al, 2007

There is considerable variability among individuals in the type, course, and severity of the manifestations, with a continuum of disease presentations ranging from the “classic” phenotype, through to a “variant”, later-onset disease. Fabry disease is X-linked and therefore all men who inherit a pathogenic mutation develop the disease (“classic” or “variant”, depending on the symptoms and level of α-Gal A activity) whilst women have a more varied presentation ranging from mild to severe (El-Abassi et al., 2014; Germain, 2010)(Section 6.1).

The symptoms of Fabry disease often begin at an early age, with the earliest manifestations typically involving the nervous system and the gastrointestinal (GI) system (Germain, 2010; Eng et al., 2007). The number and severity of symptoms increases as the disease progresses. In classic disease, severe symptoms involving the renal, cardiac, and cerebrovascular systems often develop by the time patients reach adulthood (Germain, 2010; Thomas and Hughes, 2014). A similar disease progression, but shifted to later in life, often occurs in female patients or male patients with a later onset (Mehta et al., 2004; Waldek et al., 2009; Wilcox et al., 2008). Throughout the disease process, the accumulation of GL3 and other disease substrates in cells followed by secondary tissue-damaging processes leads to progressive organ damage in both genders that can result in cardiac disease, renal disease, and stroke at an early age. End-stage renal disease (ESRD) and cardiovascular or cerebrovascular complications reduce life expectancy by 15 to 20 years (Sivley, 2013; MacDermot et al., 2001a, 2001b; Schiffmann et al., 2009; Patel et al., 2011; Germain, 2010)(Section 6.1).

The clinical profile of Fabry disease results in a substantial burden for patients and their families. Because the symptoms are often nonspecific and variable, a diagnosis often is not made until the disease has progressed for years or decades, at which point organ damage has already occurred (Germain, 2010). Pain, skin abnormalities and gastrointestinal disorders significantly contribute to reduced health-related quality of life (HRQL). As the disease progresses, there is increasing renal, cardiac and vascular involvement, including renal insufficiency, heart disease, and stroke, which represent the major source of disease-related morbidity and substantial decrements in HRQL. Patients with Fabry disease are faced with a lifelong, incurable, debilitating, progressive disease, and the physical and psychological consequences of Fabry disease affect almost all aspects of daily living and result in decreased HRQL (Sections 7 and 10).

The impact of Fabry disease goes far beyond only affecting the patient. Family members and other informal caregivers are involved in the care of patients as well as the management of their disease and experience stress and fatigue as a result of caregiving responsibilities (Street et al., 2006).

Currently, treatment for Fabry disease consists of ERT with recombinant human α-Gal A, administered via intravenous (IV) infusion every 2 weeks (Section 8.2). Two products are available in the UK:

- agalsidase alfa (Replagal®; Shire Human Genetic Therapies AB)
- agalsidase beta (Fabrazyme®; Genzyme Europe BV/Genzyme Corporation)

While ERT is effective in many patients, it does not fully address the therapeutic need in Fabry disease. In a survey of 101 UK patients with Fabry disease [Fabry Infusion Survey], [redacted] In addition ERT is associated with a risk of infusion-associated reactions (IARs) and a low but

significant risk of infections (Genzyme Therapeutics, 2014; Shire, 2006). Antibodies can develop in a substantial number of patients and interfere with ERT efficacy, exacerbate IARs, and increase the risk of clinical events (Bénichou et al., 2009; Deegan, 2012; Lenders et al., 2015).

A discrete choice experiment (DCE) was conducted in 506 members of the UK general population to understand the importance of different aspects of treatments for Fabry disease (Lloyd et al., 2016). Mode of administration, treatment-related reactions, treatment-related headaches and risk of antibody formation were all statistically significant predictors of choice. Therefore, participants placed significant value on moving to oral administration from IV, avoiding treatment related reactions and headache and also avoiding antibody formation.

In addition, the infused proteins of ERT have limited penetration to key tissues, and because of the biweekly administration schedule, patients are exposed to progressively less of the needed enzyme between infusions (Genzyme Therapeutics, 2014; Shire, 2006; Kirkegaard, 2013; Ratko et al., 2013)(Section 8.2). Caregivers also experience the burden experienced by patients in terms of inconvenience and time away from other responsibilities.

ERT for Fabry patients is in most cases delivered in the homecare setting with nursing support available for administration of infusions and requirement for temperature-controlled storage for infusion solutions.

Impact of the new technology

Migalastat has been studied in a robust clinical development program that includes four phase 3 studies (2 pivotal and 2 long-term ongoing extensions). The 2 pivotal trials of migalastat are (Section 9.3.1):

- The ATTRACT phase 3 trial, which compared patients switched from ERT to migalastat with patients who remained on ERT
- The FACETS phase 3 trial, which compared migalastat to placebo in ERT-naïve patients

The patient population in the international phase 3 studies exhibited the full spectrum of severity of clinical manifestations associated with Fabry disease and are reflective of the expected treatment population in the UK (Section 9.4.3).

The efficacy endpoints in the Phase 3 studies were focused on assessing renal function, cardiac parameters, composite clinical outcomes, and patient-reported outcomes (Section 9.4.1):

- Renal function: glomerular filtration rate (GFR) is generally recognised as the standard for measuring renal function. In patients with Fabry disease, a progressive decrease in GFR is supported by a large amount of natural history data that highlights the decline vs the normal population.
- Cardiac function: Reductions in left ventricular (LV) mass, as shown by left ventricular mass index (LVMi), have been shown to reduce risk for cardiovascular events in patients in the general population with cardiovascular disease. Reductions in LV mass have also been shown to improve outcomes in Fabry disease.
- Few trials in Fabry patients have measured rates of renal, cardiac, or cerebrovascular events, given the long-term nature of these outcomes. In ATTRACT, a composite

clinical outcome was assessed, based on the number of patients in each treatment group who experienced specific renal, cardiac, or cerebrovascular events, or death.

Trials in Fabry disease often use surrogate endpoints directly linked to the underling genetic defect and resulting disease pathophysiology. GL3 and lyso-Gb3, two of the damaging substrates that accumulate in Fabry disease, are directly linked to the underlying genetic defect that is responsible for Fabry disease and were utilised as outcome measures in the migalastat Phase 3 studies.

Progressive renal dysfunction is a major aspect of Fabry disease and is associated with the complications of end-stage renal disease, dialysis, and renal transplantation (Germain, 2010; Waldek et al., 2009; Pisani et al., 2014). In Fabry disease, slowing the progressive decline in renal function is a key treatment objective. In ATTRACT and FACETS, migalastat stabilised renal function (Germain et al., Draft Manuscript; ATTRACT Draft Manuscript)(Sections 9.6 and 9.9):

- In ATTRACT, the effects of migalastat on renal function in patients switched from ERT to migalastat were comparable to the effects of ERT in patients who remained on ERT.
- In FACETS, migalastat stabilised renal function in ERT-naive patients for up to 3 years. This is in contrast to the progressive decline that occurs in untreated patients.

Cardiac complications are the main cause of death in patients with Fabry disease (Wilcox et al., 2008; Nagueh, 2014). Left ventricular hypertrophy (LVH) is the most common cardiac manifestation in these patients and it is an important risk factor for cardiac events (Nagueh, 2014). Migalastat therapy produced significant improvement in LVMi, a key measure of left LV mass. (Germain et al., Draft Manuscript; ATTRACT Draft Manuscript)(Sections 9.6 and 9.9):

- In ATTRACT at 18 months, patients switched from ERT to migalastat had significantly decreased LVMi from baseline ($P<0.05$), while LVMi was not significantly changed from baseline in patients remaining on ERT. In a long term open label extension (30 months) patients on migalastat continued to show improvement in LVMi.
- Migalastat also significantly decreased LVMi in the FACETS trial in ERT-naïve patients at 18/24 months, and the decrease continued in the open-label extension at up to 3 years.

Furthermore, rates of renal, cardiovascular, and cerebrovascular events experienced by patients switched from ERT to migalastat in ATTRACT compared favourably with those experienced by patients who remained on ERT (29% vs 44%, respectively) (ATTRACT Draft Manuscript) (Section 9.6).

Other symptoms of Fabry disease can also negatively impact the lives of patients. In FACETS in ERT-naïve patients, migalastat significantly improved GI symptoms such as diarrhoea and indigestion (Amicus Therapeutics, 2015a). In addition, HRQL remained stable in patients switched from ERT to migalastat in ATTRACT, and improved in ERT-naïve patients in FACETS (Amicus Therapeutics, 2015a, 2015d).

Consistent with its mechanism of action, migalastat effectively reduces tissue accumulation and circulating levels of disease substrate (Sections 9.6):

- In patients switched from ERT (ATTRACT), plasma lyso-Gb3 remained low and stable for 18 months when patients were switched from ERT to migalastat.

- In ERT-naïve patients (FACETS), migalastat significantly reduced plasma lyso-Gb3 (P=0.0033) and interstitial capillary GL3 inclusions (P=0.008). Patients who switched from placebo to migalastat at 6 months for the open-label extension also showed significant decreases in plasma lyso-Gb3 (P<0.0001) and interstitial capillary GL3 inclusions (P=0.014).
- Patients receiving migalastat also had significantly qualitative reductions in GL3 levels in multiple types of renal cells over 12 months.

In both ATTRACT and FACETS, treatment with migalastat resulted in an increase in endogenous α-Gal A activity (ATTRACT Draft Manuscript; Germain et al., Draft Manuscript).

The evidence from ATTRACT is considered to be the most relevant data according the scope, since it provides a direct comparison with the relevant comparators, agalsidase alfa and agalsidase beta (ERT)(Section 9.9.3). The effects of migalastat and ERT on renal function were comparable, and longer-term stabilisation of renal function by migalastat has been shown over 3 years of treatment. Patients switched from ERT to migalastat exhibited statistically significant decreases in LVMi from baseline, with a clinically relevant improvement in particular in patients with existing cardiac hypertrophy. This reduction on LVMi has also shown to be continued over 30 months in the open-label extension study (Bichet et al., 2016). Conversely, in ATTRACT, no reduction in LVMi was detected in patients that remained on ERT. Migalastat also compared favourably to ERT in the incidence of Fabry-associated clinical events (renal, cardiac or cerebrovascular event or death; composite 29% vs. 44%), which are the main sources of morbidity and mortality in patients with this disease (ATTRACT Draft Manuscript).

Migalastat is well-tolerated, with headache the only adverse event (AE) ≥10% in clinical trials. In ATTRACT, the frequency of headache was similar in patients who were switched to migalastat and those who remained on ERT (25% vs. 24% respectively) (Section 9.7.2).

In patients with amenable mutations (estimated to be between 30–50% of currently diagnosed patients with Fabry disease), migalastat, administered orally every other day, has clear advantages over ERT (Amicus Therapeutics, 2015c):

- With regard to the burden of treatment, an orally administered medication would be a significant benefit to patients and their families over ERT infusions as demonstrated in the DCE, in which participants placed significant value on moving to oral administration from IV.
- As an oral therapy migalastat does not result in IARs that occur commonly with ERT (Genzyme Therapeutics, 2014; Shire, 2006), which were found to be a statistically significant predictor of choice in the DCE.
- As a small molecule, migalastat does not have the risk of immunogenicity that is present with ERT.
- Oral treatments eliminate the risk of infections associated with vascular access that is required for ERT administration.
- As a small molecule, migalastat has broad tissue distribution (Amicus Therapeutics, 2016c). It is anticipated that this characteristic may offer enhancement of α-Gal A activity levels in multiple organs (e.g., heart) and tissues. Migalastat also has distribution across the blood-brain barrier (Khanna et al., 2010).

- Every-other-day oral migalastat provides more consistent chaperoning of endogenous α-Gal A to the lysosome that is closer to natural enzyme trafficking than every-other-week infusions of manufactured ERT (Johnson et al., 2016).

Cost to the NHS and Personal Social Services

The prevalence of Fabry disease was obtained from a report by the Northern Genetics Service in the North of England (Brennan and Parkes, 2014), which estimated a theoretical prevalence of symptomatic Fabry disease to be 1 in 64,600 (0.002%) (Section 13.1). The diagnosis rate was derived from the number of patients enrolled in the Fabry Disease Registry and Fabry Outcome Survey compared to the theoretical prevalence, equating to 78.6%. Thus it is expected that there are 672 diagnosed patients in England, of which 60% are currently receiving ERT. Of these patients:

- 30-50% have amenable mutations (midpoint of 40% is used in base case) (Benjamin et al., 2009; Filoni et al., 2010; Germain et al., 2012; Shabbeer et al., 2006; Ishii et al., 2007; Wu et al., 2011).
- 97% of treated patients are aged 16 or over (based on longitudinal cohort study of people with lysosomal storage disorders in the UK) (Wyatt et al., 2012)
- 91% of treated patients do not have ESRD: average of a reported 83% for males and 99% for females, obtained from an analysis of UK Fabry Registry data (Mehta et al., 2004)

Based on the above, it is anticipated 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.

Market uptake in the prevalent population is estimated to be [redacted] in year 1, [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5 (Section 13.2). The market uptake in the incident population is expected to be higher given the more convenient administration of migalastat: [redacted] in year 1, [redacted] in year 2 with [redacted] increased uptake per annum thereafter. This equates to the following numbers of patients being treated with migalastat: [redacted] in year 1, [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5.

The annual cost of migalastat at the list price is £210,000 per patient per year. NHS England has tendered a national contract for ERT that includes a confidential discount on the list price; in the base case analysis it is assumed that this discount is 3% (Section 12.3.5). Clinical expert opinion suggests that the mean weight of Fabry patients is the same as the general population. This equates to an annual cost of £126,689 for agalsidase beta and £134,756 for agalsidase alfa. Clinical experts estimate the market shares for ERT are 70% agalsidase alfa and 30% agalsidase beta. Total incremental treatment costs following the introduction of migalastat are expected to be [redacted] in year 1, increasing to [redacted] in year 5.

The biggest cost savings with migalastat are expected to come from reduction in administration costs (Section 13.4). The cost of homecare has been contracted by NHS England under a confidential national tender but expert opinion suggests that the cost is £200 per bi-weekly infusion, equating to a cost per patient per year of £5,200. In addition, expert opinion has suggested 50% of patients have a nurse to administer infusions, at an estimated cost of £165 per infusion. Total savings from administration costs following the introduction of

migalastat are expected to be £367,608 in year 1, increasing to £999,583 in year 5. The total savings over 5 years is expected to be £4 million.

The total budget impact of migalastat is therefore expected to be [redacted] in year 1, [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5.

Whilst the number of eligible symptomatic patients in England is known, there is uncertainty regarding (Section 13.8):

- The proportion of patients with amenable mutations
- The market uptake of migalastat
- The cost of a nurse administering an infusion of ERT at home
- Since ERT is a weight-based dose, the cost of ERT acquisition is sensitive to weight
- Since ERT is subject to tender, the exact price paid is unknown
- Due to lack of data on incidence, incidence is driven by population growth
- Mortality is not modelled explicitly in the model due to the short time horizon of the analysis.

Value for money

A cost-consequence analysis has been created to evaluate migalastat compared to ERT from the perspective of the NHS and personal social services. The model structure was based on a published Dutch cost-effectiveness evaluation of Fabry disease that captures the key symptoms and complications of Fabry disease: pain, renal disease, cardiac complications and stroke (Section 12.1.3). Based on the observations from ATTRACT, the treatment effect of migalastat is assumed to be equal to ERT and thus the cohorts progress through the health states at the same rate. This is considered to be a conservative assumption given that, in ATTRACT, results for LVMi and the composite endpoint of cardiac/renal/cerebrovascular events were in favour of migalastat rather than ERT (Section 9.6), suggesting migalastat could slow progression between health states more than ERT.

In clinical trials, a small proportion of patients discontinued ERT treatment due to infusion associated reactions (Banikazemi et al., 2007), which would not occur with migalastat given that it is an oral regimen. Based on clinical expert opinion, the model assumes a probability of discontinuation of 0.05% per annum with ERT and 0% with migalastat (Section 12.2.1). With the modelled assumption that migalastat and ERT are equally efficacious but have slightly different discontinuation rates, the only difference in outcomes from the model in terms of health state transition is that migalastat patients will benefit from staying on treatment slightly longer and thus marginally improved outcomes. This difference in discontinuation results in less than 0.01 discounted incremental QALYs (Section 12.5.4).

The greatest modelled benefit of migalastat in terms of QALYs is from preferences for an oral treatment rather than ERT infusions. The DCE results indicate that infusions for Fabry disease are associated with disutility of 0.052 per annum, without factoring in the HRQL impact of IARs and the risk of developing antibodies (Section 10.1.9)(Lloyd et al., 2016). Over the course of the model, this equates to a discounted QALY gain with migalastat of 0.97. Thus the total incremental QALY gain for migalastat compared to ERT is 0.98. In a scenario

incorporating all statistically significant attributes from the DCE, the QALY gain for migalastat increased to 2.23.

As stated above, NHS England has tendered a national contract for ERT that includes a confidential discount on the list price; in the base case analysis it is assumed that this discount is 3%, which is varied between 0% and 7% in sensitivity analyses (Section 12.3.5). Clinical experts estimate the market shares for ERT are 70% agalsidase alfa and 30% agalsidase beta. Based on this assumed discount and market share the total discounted lifetime cost of ERT treatment is £2,581,037. Comparatively, at the list price migalastat is associated with lifetime treatment costs of £3,989,923.

As detailed above, the biggest cost savings with migalastat are expected to come from reduction in administration costs (Section 12.3.6). The total discounted lifetime savings in administration costs are estimated to be £140,149 per patient. Factoring in savings from administration costs and additional minor savings from fewer adverse events, the resulting total incremental lifetime costs of migalastat (at list price) compared to ERT are £1,268,674.

Impact of the technology beyond direct health benefits

Fabry disease can affect all aspects of daily life and can lead to issues in social interactions, school attendance, sports participation, and employment opportunities (Sivley, 2013; Laney et al., 2010). Provision of an additional effective, more convenient treatment option is expected to help patients stay in employment for longer and offset costs due to loss of employment or reduction in working days.

[redacted]

Feedback from the Fabry disease Patient Survey (2016) confirmed the negative impact of ERT:

- “I have to plan my social life around my treatment, it restricts greatly going to our holiday home.”
- “I have to have time off work for ERT treatment, I don’t want to go out after my treatment and that impacts on daily living”.

As an oral treatment, migalastat offers a more convenient alternative to ERT that will avoid interruptions to working life, loss of productivity from ERT infusions, as well as avoiding IARs and development of neutralising antibodies (Parini et al., 2010).

Insights from the aforementioned DCE indicate a significant preference for an oral treatment for Fabry disease compared to IV infusion.

In addition, time taken by caregivers to assist or supervise infusions may be significant and would be saved if replaced by an oral therapy. In the Fabry Infusion Survey described in Section 7 the average infusion time for patients on bi-weekly ERT was [redacted] (Amicus Therapeutics, 2015e).

The impact of the technology on the delivery of the specialised service

No additional facilities, technology or infrastructure are required for the introduction of migalastat. Migalastat is an oral therapy and will be prescribed and monitored within existing services for lysosomal storage disorders (LSDs).

No additional genetic testing is required by the NHS to identify patients eligible for migalastat. Standard genetic testing for Fabry disease can identify the mutation, and Amicus Therapeutics has developed a database of mutations amenable to migalastat, a process that is on-going since not all mutations have been tested to date. The testing of new samples for mutations that are amenable to migalastat would be performed regularly by Amicus at the company's expense and the list of amenable mutations will be updated.

The use of migalastat in patients who would otherwise receive ERT would mean patients having fewer invasive intravenous infusions and therefore the number of homecare nurses required to administer, and re-train venous access technique for ERT infusions in Fabry patients would be reduced.

Conclusion

Migalastat is a first-in-class, orally administered, small molecule that selectively binds and stabilises mutant α-Gal A in patients with Fabry disease with mutations amenable to chaperone therapy. Chaperone therapy allows the body to use its own endogenous enzyme, rather than one that is artificially introduced as in the case of ERT. Migalastat provides targeted, personalised monotherapy with demonstrated efficacy and avoids the burdens associated with ERT infusions. Because migalastat acts only in those patients with Fabry disease with amenable mutations, the patient population eligible for migalastat is well defined. In these patients, migalastat provides consistent increases in α-Gal A activity in a wide distribution of tissues throughout the body, where it decreases substrate inclusions and increases α-Gal A activity. In both patients switched from ERT and patients naïve to ERT, migalastat significantly decreased LVMi and stabilised renal function. The combination of efficacy, safety, and tolerability demonstrated with migalastat offers the potential to reduce the healthcare costs of progressive, irreversible end-organ damage in Fabry disease. Availability of migalastat would provide an additional treatment choice for patients with a convenient oral administration. It has been shown that an orally administered treatment for Fabry disease is significantly preferred to intravenous infusion (Lloyd et al., 2016).

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1.1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with Fabry disease with a confirmed GLA mutation that is amenable to migalastat in vitro	No variation.	
Intervention	Migalastat (Galafold™)	No variation.	
Comparator(s)	• Agalsidase alfa • Agalsidase beta	No variation.	
Outcomes	• 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)	No variation.	

Subgroups to be considered	None specified	No variation.	
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	No variation.	
Cost to the NHS and PSS, and Value for Money	• Budget impact in the NHS and PSS, including patient access agreements (if applicable) • Robustness of 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) • Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)	No variation.	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • Staffing and infrastructure requirements, including training and planning for expertise.	No variation.	
Special considerations, including issues related to equality		No variation.	

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Galafold™

Approved name: Migalastat

Therapeutic class: Pharmacological chaperone (WHO ATC code not yet assigned)

2.2 What is the principal mechanism of action of the technology?

Fabry disease is a progressive X-linked lysosomal storage disorder that affects males and females. Fabry disease-causing mutations in the *GLA* gene result in a deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A) that is required for glycosphingolipid substrate (e.g., GL3, lyso-Gb3) metabolism. Reduced α-Gal A activity is, therefore, associated with the progressive accumulation of substrate in vulnerable organs and tissues, which leads to the morbidity and mortality associated with Fabry disease (Amicus Therapeutics, 2016c).

The majority of α-Gal A mutations result in the production of abnormally folded and unstable mutant α-Gal A. The mutant α-Gal A is degraded before it can be trafficked to the lysosome, but biochemical analysis has shown that some misfolded enzymes have an intact active site and are capable of enzymatic activity, and it is only their inability to reach the lysosome that results in a deficit in α-Gal A activity.

Migalastat is a targeted, personalised therapy. Migalastat is a pharmacological chaperone that is designed to selectively and reversibly bind with high affinity to the active sites of certain mutant forms of α-Gal A, the genotypes of which are referred to as amenable mutations. Migalastat binding stabilises these mutant forms of α-Gal A in the endoplasmic reticulum and facilitates their proper trafficking to lysosomes where dissociation of migalastat restores α-Gal A activity, leading to the catabolism of GL3 and related substrates for normal function (Amicus Therapeutics, 2016c). Chaperone therapy allows the body to use its own endogenous enzyme, rather than one that is artificially introduced as in the case of ERT.

2.3 Please complete the table below.

Table A2.1: Dosing Information of technology being evaluated

Pharmaceutical formulation	Hard capsule. Each capsule contains migalastat hydrochloride (HCl) equivalent to 123 mg migalastat. Migalastat 123 mg is equivalent to 150 mg migalastat HCl, the formulation and dose used in the phase 3 clinical trials
Method of administration	Oral
Doses	The recommended dose of migalastat in adults and adolescents ≥16 years is 1 capsule (123 mg migalastat) orally once every other day at the same time of day. Migalastat should not be taken within 2 hours before and after food. The capsule should be swallowed

	whole and must not be cut, crushed, or chewed.
Dosing frequency	Once every other day
Average length of a course of treatment	Not applicable. Long-term chronic therapy.
Anticipated average interval between courses of treatments	Not applicable. Long-term chronic therapy.
Anticipated number of repeat courses of treatments	Not applicable. Long-term chronic therapy.
Dose adjustments	No dosage adjustment is required based on age (i.e. in the elderly). Migalastat is not recommended for use in patients with Fabry disease who have an eGFR <30 mL/min/1.73 m^2. No dosage adjustment is required in patients with hepatic impairment. If a dose is missed, patients should resume taking migalastat at the next dosing day and time (it should not be taken 2 days in a row).

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Positive CHMP opinion expected end of March 2016, with full marketing authorisation expected in May or June 2016.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Migalastat is expected to be commercially available in the UK from May or June 2016.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

No.

3.4 If the technology has been launched in the UK provide information on the use in England.

N/A

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Table A4.1: Migalastat clinical study programme

Trial no. (acronym)	Study Design	Intervention	Population	Reference
AT1001-012 ATTRACT NCT01218659	Phase 3 study: 18-month active-controlled, randomised, open-label, multinational study vs. ERT followed by a 12-month open label extension (OLE) in which all patients received migalastat (n=60)	Migalastat hydrochloride 150 mg once every other day (n=36) Enzyme Replacement Therapy (ERT) – either agalsidase alfa or beta (n=24)	ERT-experienced patients *(≥12 months prior continuous ERT with dose and regimen stable for 3 months and ≥80% of currently labelled dose and regimen)* either: - Switched from ERT to migalastat HCl 150 mg once every other day - Remained on ERT	ATTRACT Draft Manuscript. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in patients with Fabry disease: 18-month results from the phase 3 ATTRACT study Amicus Therapeutics. EMA submisison. 2.7.3 Summary of Clinical Efficacy 2015.
AT1001-011 FACETS NCT00925301	Phase 3 study: 6-month randomised, placebo-controlled double-blind period followed by a 6-month OLE during which all patients received migalastat and an optional 12-month OLE (n=67)	Migalastat hydrochloride 150 mg once every other day (n=34) Placebo (n=33)	Patients who were either ERT-naïve or had no ERT for ≥6 months were randomised to: - Migalastat HCl 150 mg once every other day - Placebo	Germain D, et al. (Submitted Manuscript) Efficacy and safety of migalastat, an oral pharmacological chaperone for Fabry disease. Amicus Therapeutics. EMA Submisison. 2.7.3 Summary of Clinical Efficacy 2015.
AT1001-041	OLE study for	Migalastat	OLE study for	Amicus

NCT01458119	patients in ATTRACT, FACETS, and FAB-CL-205 [redacted] Terminated for administrative reasons (66 patients are continuing in AT1001-042).	hydrochloride 150 mg once every other day	patients in ATTRACT, FACETS, and FAB-CL-205 Study was terminated for administrative reasons	Therapeutics. EMA Submisison. 2.7.3 Summary of Clinical Efficacy 2015
AT1001-042 NCT02194985	OLE successor to AT1001-041 Study is ongoing [redacted]	Migalastat hydrochloride 150 mg once every other day		Amicus Therapeutics. 2.7.3 Summary of Clinical Efficacy 2015

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

Scottish Medicines Consortium (SMC) – migalastat has not been reviewed by the SMC to date. Submission to the SMC is anticipated during 2016.

All Wales Medicines Strategy Group (AWMSG) – Migalastat has not been reviewed by the AWMSG to date. No date for submission has been set as yet.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

It is not anticipated that this evaluation could exclude or lead to recommendations that have an adverse impact on people with a particular disability. The availability of an oral therapy compared to those currently available that are intravenously administered would offer additional choice and benefits for those patients who would prefer the convenience of an oral treatment option.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Rare diseases have a considerable emotional impact on patients and caregivers (Genetic Alliance, 2013). For those rare disease patients where treatment options are limited, overall they worry more, feel more depressed, interact less, and feel more isolated from family and friends compared to patients with rare diseases for which there are available treatments (Genetic Alliance, 2013).

Whilst agalsidase alfa and agalsidase beta have been available and commissioned by NHS England for many years, both of these therapies are intravenously administered, requiring regular lengthy infusions. A positive review of migalastat by NICE will facilitate and ensure equity of access to an oral therapy with the convenience it brings for patients with a genetic disease and ensure that patients with rare diseases are not discriminated against.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Overview of Fabry disease

Fabry disease is a rare genetic disease caused by a mutation in the gene *GLA* such that an abnormal form of alpha-galactosidase A (α-Gal A) is produced that is non-functional or only partially functional. Over 800 pathogenic mutations of *GLA* have been identified with the majority of mutations resulting in α-Gal A that is misfolded, preventing its trafficking from the endoplasmic reticulum to the lysosome. Decreased enzyme activity in the lysosome results in the accumulation of disease substrates, including globotriaosylceramide (GL3/GB3, referred to in this submission as GL3) and globotriaosylsphingosine (lyso-Gb3), in tissues throughout the body. Over the years, the accumulation of these products damages cells and leads to progressive and irreversible organ damage, typically involving the nervous system, endothelium, kidney, and heart, as well as other tissues.

Patients with Fabry disease experience cardiac disease, renal disease, and stroke at an early age, causing early chronic illness. These severe complications also result in a reduced life expectancy compared with the general population: 20 years less in men and 15 years less in women (Waldek et al., 2009; MacDermot et al., 2001a, 2001b; Schiffmann et al., 2009).

Underlying cause of the disease

Fabry disease results from a mutation in a single gene, the *GLA* gene, which is located on the X chromosome and codes for α-Gal A, an enzyme that breaks down glycosphingolipids in cell lysosomes (El-Abassi et al., 2014; Guce et al., 2011; Ishii, 2012).

A pathogenic *GLA* mutation results in a complete or partial reduction in α-Gal A activity where the degree to which α-Gal A activity is reduced determines the severity of the disease (Sivley, 2013; Germain, 2010). As such, there is considerable variability among individuals in the type, course, and severity of the manifestations (Thomas and Hughes, 2014) (see Table B6.1). All males who inherit a pathogenic mutation develop Fabry disease, which is sometimes categorised as "classic" or "variant", depending on the symptoms and level of α-Gal A activity (El-Abassi et al., 2014; Germain, 2010). Males with classic Fabry disease may have no or very low levels of α-Gal A activity and males with variant phenotypes usually have higher but still below normal enzyme activity (El-Abassi et al., 2014). Female patients have even more varied presentation ranging from asymptomatic to symptoms as severe as in males with classic disease (Germain, 2010). Female patients may have levels that range from deficient to normal due to X-inactivation (lyonization), a process in which one X chromosome is randomly inactivated in each cell, producing a mixture of cells expressing normal wild type α-

Gal A and cells expressing mutant α-Gal A (El-Abassi et al., 2014). Skewed X-inactivation in tissues and organs results in more or less expression of the chromosome carrying the mutated gene; greater expression of the mutated gene is reflected in reduced α-Gal A activity and greater disease severity (El-Abassi et al., 2014; Sivley, 2013).

Table B6.1: Fabry disease phenotypes

Phenotype	Features
Classic Fabry presentation	• Occurs in males with full spectrum of symptoms (neurologic, cerebrovascular, cutaneous, renal, cardiovascular, auditory dysfunction, GI) • Usually has an early onset • α-Gal A activity usually absent or very low • Females may also present with the classic phenotype at a young age
Variant, atypical, or later onset Fabry disease	• Manifestations may be limited mainly to 1 organ system, but a full spectrum of symptoms may also appear with later onset • Residual α-Gal A activity present (2% to 20% of normal) • Usually has a later onset (e.g., in fourth to sixth decades) • More prevalent than classic Fabry disease • In women, onset is typically later (mean age 20 years) and presentation varies from mild to severe
• Cardiac variant	• Manifests with nonobstructive hypertrophic cardiomyopathy and MI • Most widely reported variant
• Renal variant	• Renal disease presents in midlife and progresses to ESRD

α-Gal A=alpha-galactosidase A; ESRD=end-stage renal disease; GI=gastrointestinal; MI=myocardial infarction.
Sources: Germain, 2010; El-Abassi et al., 2014; Sivley, 2013; Deegan et al., 2006

Over 800 different pathogenic mutations of the *GLA* gene have been described, including splicing mutations, missense and nonsense point mutations, large and small deletions, and small insertions (El-Abassi et al., 2014; Amicus Therapeutics, 2015b). Many mutations are unique, occurring in only one family (Mahmud, 2014; Germain, 2010). The large number of mutations and the extensive range and variability of clinical features have made it difficult to associate specific mutations with specific phenotypes (Thomas and Hughes, 2014).

Overall, accumulating evidence indicates that genotype is not predictive of disease severity. A number of studies show that patients with the same genotype may have varying levels of symptoms, severity and organ system involvement (Patel et al., 2015; Niemann et al., 2014) and that even patients with ≥20% of α-Gal A activity can have severe and multi-organ disease (Lukas et al., 2016). It is important to note that disease severity and symptoms are the most relevant factors in determining the need for treatment and not necessarily the presence of multi-organ involvement (see Section 8).

Normally, α-Gal A is produced in the endoplasmic reticulum and transported (trafficked) to the lysosome, where it catalyses the breakdown of glycosphingolipid compounds such as GL3 and lyso-Gb3 (Thomas and Hughes, 2014; Ishii, 2012). The function of any protein is partially determined by its 3-dimensional structure, termed its folding. The most common pathogenic *GLA* mutations lead to misfolding of the α-Gal A protein, which prevents it from being trafficked from the endoplasmic reticulum to the lysosome (Thomas and Hughes, 2014; Guce et al., 2011). Consequently, GL3, lyso-Gb3, and other glycosphingolipids progressively

accumulate, eventually damaging the cell and disrupting cell function (Thomas and Hughes, 2014; Sivley, 2013; Germain, 2010).

Many types of cells are affected and a number pathophysiologic processes are involved. It has traditionally been thought that the accumulation of disease substrates led to vessel occlusion and tissue ischemia, which in turn led to fibrosis (the replacement of normal cells with fibrotic tissue) (Eng et al., 2006; Weidemann et al., 2013b). It is now thought that the accumulation of disease substrates also promotes the release of secondary mediators of injury from the affected cells, and that ischaemia also promotes the release of secondary mediators. These numerous secondary mediators result in inflammation and a variety of other effects, ultimately producing organ damage (Table B6.2) (El-Abassi et al., 2014; Thurberg et al., 2009; Eng et al., 2006; Weidemann et al., 2013b). The varied physiologic responses to GL3 accumulation increase the heterogeneity of disease presentation and also contribute to disease progression (Eng et al., 2006).

Table B6.2: Pathophysiological findings in Fabry disease

Organ system	Cell types potentially affected	Selected pathophysiologic findings
Kidney	Podocytes, glomerular endothelium, epithelium of Bowman's capsule, loops of Henle and distal tubule, arterial and arteriolar smooth muscle and endothelium, interstitial cells	Glomerular sclerosis, tubular atrophy, interstitial fibrosis
Cardiac	Cardiomyocytes, conduction system cells, vascular endothelial and smooth muscle cells, valvular fibrocytes	LVH, HF, stenosis of epicardial vessels, atherosclerotic plaques, thrombotic and thromboembolic complications
Neurologic	Neurovascular endothelial cells, neurons within CNS and PNS, including dorsal root and autonomic ganglia	Ischaemic injury and metabolic failure resulting in functional disruption of neuronal cells, and loss of small myelinated and unmyelinated fibres
Dermatologic	Vascular endothelial cells, smooth muscle cells, fibroblasts, sweat glands	Weakening of capillary wall and vascular ectasia within epidermis, narrowing of small blood vessels around sweat glands
Ophthalmologic	Epithelial cells in the cornea, lens, vascular endothelial cells	Streaks in corneal epithelium, vasculopathy of the conjunctival and retinal vessels, central retinal artery occlusion, reduced lacrimal secretion
Pulmonary	Airway epithelial cells, vascular endothelial cells, smooth muscle cells	Airway narrowing, capillary blockage
GI	Vascular endothelial cells in the small intestine, colon and rectum; smooth muscle cells; autonomic nerve ganglia in the intestinal wall; small unmyelinated neurons	Narrowing of mesenteric small blood vessels
Auditory	Vascular endothelial cells, smooth muscle cells, ganglion cells	Narrowing or total occlusion of cochlear vessels; ischaemic auditory neuropathy

CNS=central nervous system; GI=gastrointestinal; HF=heart failure; LVH=left ventricular hypertrophy; PNS= peripheral nervous system.
Source: Eng et al., 2006

Onset and course of disease

Most patients remain clinically asymptomatic during the first years of life, although the accumulation of GL3 and other disease substrates begins in utero (El-Abassi et al., 2014;

Sivley, 2013; Germain, 2010). The degree of accumulation depends on the level of residual α-Gal A activity present in an individual (Sivley, 2013). In an analysis of 1,765 patients in the Fabry Registry, the median age at the onset of the initial symptoms was 9 years in males and 13 years in females (see Table B6.3 and Figure B6.1), although there is variability (Eng et al., 2007; Kusano et al., 2014; Germain, 2010). The earliest manifestations typically involve the nervous system and the gastrointestinal (GI) system (Eng et al., 2007; Germain, 2010).

Patients often spend many years with undiagnosed Fabry disease, during which time progressive, irreversible end-organ damage is occurring; since the symptoms are nonspecific and variable, and because many physicians may not be familiar with this rare disease. The diagnostic process can be extensive and prolonged, with patients often misdiagnosed.

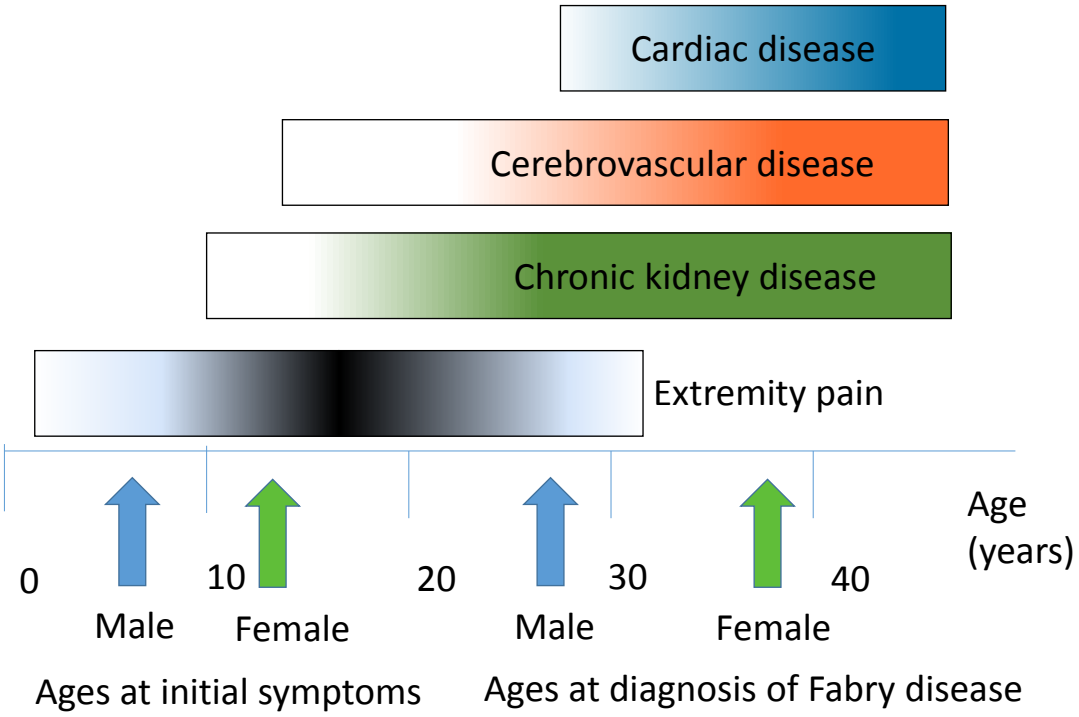
Table B6.3: Fabry disease manifestations onset by age in 1,765 patients

	Males (n=713)		**Females (n=430)**	
Manifestations	**Median age at onset**	**% with symptom**	**Median age at onset**	**% with symptom**
Neurologic (other than pain)	8 years	12%	12 years	12%
GI	8 years	19%	14 years	13%
Pain	9 years	62%	10 years	41%
Skin	9 years	31%	17 years	12%
Ophthalmologic	9 years	11%	16 years	12%
Cerebrovascular	10 years	5%	26 years	4%
Respiratory	11 years	3%	30 years	2%
Cardiovascular	12 years	13%	32 years	10%
Renal	20 years	17%	28 years	11%

GI=gastrointestinal. Source: Eng et al., 2007

Fabry disease has a progressive course, with the number and severity of symptoms and the number of organ systems progressively increasing over time (Kes et al., 2013; Thomas and Hughes, 2014; Sivley, 2013; Mehta et al., 2004; Kusano et al., 2014; Germain, 2010). Figure B6.1 depicts the onset and progression of some of the key manifestations in Fabry disease, with the darker gradient indicating more severe disease (Kusano et al., 2014). The number of organ systems involved increases with age in both males and females (Mehta et al., 2004). While substrate accumulation begins in utero, clinical symptoms such as pain, GI dysfunction, anhidrosis, and angiokeratoma appear in early childhood in males. By adulthood, severe symptoms involving the renal, cardiac, and cerebrovascular systems often develop (Thomas and Hughes, 2014; Germain, 2010). A similar disease progression with associated long-term complications, but shifted to later in life, often occurs in female patients or male patients with a later onset.

Figure B6.1: Typical onset and progression of symptoms in Fabry disease



Source: Kusano et al., 2014

Disease morbidity

Fabry disease can present with a variety of manifestations and the type and severity of the manifestations can vary significantly among patients (see Figure B6.1 and Table B6.3) (El-Abassi et al., 2014; Germain, 2010). The frequency of different manifestations included in the Fabry Outcome Survey which included 366 European patients is presented in Table B6.4 (Mehta et al., 2004).

Table B6.4: Frequency of manifestations in 366 patients with Fabry disease

Manifestation	% of males with manifestation (n=201)	% of females with manifestation (n=165)
Neurologic	84%	79%
• Neuropathic pain	76%	64%
Dermatologic	78%	50%
Cardiac	69%	65%
• LVH	46%	28%
Ocular	62%	53%
Auditory	57%	47%
GI	55%	50%
Renal	50% (of all patients)	
• Proteinuria	44%	33%
• ESRD	17%	1%
Vascular	45%	35%
Fatigue	24%	28%
Stroke or TIA	12%	27%

ESRD=end stage renal disease; GI=gastrointestinal; LVH=left ventricular hypertrophy; TIA=transient ischemic attack.
Source: Mehta et al., 2004

Even patients with substantial residual α-Gal A activity (≥20%) often still experience significant symptoms in multiple organ systems. A study in 61 male and 116 female patients with ≥20% residual α-Gal A activity (median 51%) showed that 20% of female and 23% of male patients had symptoms in 2 organ systems, and that 44% of female and 30% of male patients had symptoms in multiple organ systems (Lukas et al., 2016).

The following paragraphs describe the key symptoms of Fabry disease in more detail.

Neurologic Symptoms

Peripheral neuropathy is a common early feature of Fabry disease; symptoms include neuropathic pain (bilateral) beginning in the palms of the hands and soles of the feet, reduced temperature sensation in the hands and feet, reduced cold tolerance, and reduced vibratory perception (El-Abassi et al., 2014; Sivley, 2013; Germain, 2010). As noted in Table B6.4, neuropathic pain was the most common neurologic symptom in a study of 366 patients from the Fabry Outcome Survey (Mehta et al., 2004). The pain can be episodic or chronic. Episodic pain (termed Fabry's crises) is characterised by burning pain starting in the extremities (e.g., palms and soles) that may become sufficiently severe to confine the patient to bed (Burlina et al., 2011). Patients may require opioids or anticonvulsants for pain control, and sometimes require hospitalisation (MacDermot et al., 2001b). These crises may be precipitated by exercise, fatigue, and other factors, occur 4 to 6 times per year, and may last for hours to weeks (Pagnini et al., 2011). The chronic pain element of the disease is comprised of tingling and burning paraesthesia's (El-Abassi et al., 2014; Sivley, 2013; MacDermot et al., 2001b; Germain, 2010). In many cases, the pain is not recognised as a symptom of Fabry disease, which leads to diagnostic delays, sometimes until the child is an adult with more severe disease (Pagnini et al., 2011).

Neurologic symptoms may also involve the autonomic nervous system. Manifestations can include reduced saliva and tear formation, anhidrosis or hypohidrosis (absent or reduced

sweating), cardiac dysrhythmia, impaired pupillary constriction, and intestinal dysmotility (El-Abassi et al., 2014; Burlina et al., 2011). Orthostatic hypotension and syncope have been reported in some patients with advanced disease (El-Abassi et al., 2014; Burlina et al., 2011).

Psychiatric disorders and social problems have also been noted in patients with Fabry disease, although the data are limited (Sivley, 2013; Germain, 2010). In the largest survey of psychiatric disorders in patients with Fabry disease (184 of 296 patients responding), responses consistent with clinically significant depression were reported by 46%, including 28% with severe clinical depression (Cole et al., 2007). Data from 2 smaller studies are similar. In one of these studies (N=30), 58% had scores indicating depression and 39% had scores consistent with borderline or full blown generalised anxiety disorder (Laney et al., 2010). In the other study (N=16), 10 patients had depressive symptoms (Segal et al., 2010). However, it is thought likely that depression is a reaction to the symptoms of Fabry disease, rather than a symptom of the disease itself (Bolsover et al., 2013). Furthermore, because the pervasive, severe symptoms of Fabry disease can affect all aspects of daily life, it is thought that they can impair social-adaptive functioning, leading to issues in social interactions, school attendance, sports participation, and employment opportunities (see Section 7)(Sivley, 2013; Laney et al., 2010).

In addition, there are some limited data that Fabry disease can affect some aspects of cognitive function. A meta-analysis suggested that executive function, information processing speed, and attention may be impaired in patients with Fabry disease (Bolsover et al., 2013).

Cardiovascular disease

Cardiac symptoms are reported in 40% to 60% of patients with Fabry disease, with onset generally in the third to fourth decades (El-Abassi et al., 2014; Germain, 2010). That is, patients with Fabry disease experience serious cardiac disease far earlier than individuals in the general population. Overall, cardiovascular disease is one of the leading causes of reduced life expectancy in untreated patients with Fabry disease (Germain, 2010). Presenting symptoms of cardiovascular involvement can include palpitations, chest pain, and dyspnoea. However, some patients are asymptomatic, even though disease substrates are accumulating in cardiomyocytes and the endothelial cells of the arteries and capillaries (Nagueh, 2014). Left ventricular hypertrophy (LVH), an increase in mass of the left ventricle (LV) that results in cardiac dysfunction, is a key finding in these patients (Nagueh, 2014). LVH has been shown to be the greatest risk factor for serious cardiac events in patients with Fabry disease (Patel et al., 2011). A key pathologic change is the substitution of fibrotic tissue for myocardial tissue, and over time this process progresses to congestive heart failure (CHF) (El-Abassi et al., 2014; Germain, 2010). Myocardial ischemia, resulting in myocardial infarction (MI), can occur (Patel et al., 2011). Other manifestations can include mitral valve regurgitation and electrocardiogram (ECG) abnormalities (Nagueh, 2014). Serious arrhythmias can also occur, resulting in sudden cardiac death (Germain, 2010).

As noted previously, some patients have α-Gal A mutations associated with a later-onset, predominantly cardiac phenotype of Fabry disease. However, a study of 207 patients (72% with the classic phenotype and 28% with a cardiac phenotype) showed that cardiac symptoms and their progression were not different between the classic and cardiac phenotype groups (Patel et al., 2015).

Renal disease

Progressive renal impairment is a prominent feature of Fabry disease. Renal failure is the primary cause of death in untreated patients who do not receive chronic haemodialysis or renal transplantation (Pisani et al., 2014; Mahmud, 2014; Germain, 2010). Numerous renal cells and tissues are damaged by GL3 accumulation, as described in Table B6.2 (El-Abassi et al., 2014; Pisani et al., 2014; Germain, 2010). Two key findings resulting from GL3 accumulation are glomerulosclerosis (formation of scar tissue in the filtering units of the kidney) and interstitial fibrosis (replacement of functioning tissue with fibrotic tissue); both of these are irreversible changes in the kidney that lead to kidney dysfunction (Pisani et al., 2014). Renal disease usually first manifests in childhood and adolescence as glomerular hyperfiltration (Pisani et al., 2014). Microalbuminuria, followed by proteinuria, and elevated serum creatinine levels are seen in the second to third decades, and azotemia occurs in the third to fifth decades (El-Abassi et al., 2014; Germain, 2010). In a study of 462 untreated adult patients (74% women), the urinary protein to creatinine ratio was a good predictor of renal disease progression (Wanner et al., 2010). In males, end-stage renal disease (ESRD) generally develops in the third to fifth decades (El-Abassi et al., 2014; Germain, 2010).

Renal damage also predicts cardiovascular disease: in a 10-year study of 25 male patients treated with ERT, the presence of ESRD was the strongest predictor of cardiac disease progression (Talbot et al., 2015).

Cerebrovascular disease

Early cerebrovascular disease is a common complication of adult patients with Fabry disease. Manifestations include headaches, vertigo, and dizziness, as well as more serious conditions such as transient ischemic attacks (TIAs), ischemic strokes, and vascular dementia (El-Abassi et al., 2014; Sivley, 2013; Germain, 2010). In an analysis of 388 patients (56% male) in the Fabry Outcome Survey, 51 patients (13%) had either a stroke or TIA, including 12 males and 10 females younger than 44 years of age (Mehta and Ginsberg, 2005). Compared to the general population, the frequency of stroke was about 12 times greater in males 25 to 44 years old (Mehta and Ginsberg, 2005). In another study (N=43), 24% of the male patients and 28% of the female patients had either a TIA or stroke; a total of 64% of the male patients and 72% of the female patients had abnormal findings on brain magnetic resonance imaging (Buechner et al., 2008).

GI dysfunction

As noted previously, GI symptoms may first appear in childhood and persist through adulthood (Germain, 2010). In a review of 342 patients not treated with ERT, GI symptoms were reported in 52% of patients and were more frequent in children compared to adults (60.8% vs. 49.8%). The most frequent symptoms were abdominal pain, diarrhoea, constipation, nausea and vomiting. They often occur following meals, sometimes making children reluctant to eat (MacDermot et al., 2001b). These GI symptoms may lead to anorexia and weight loss (MacDermot et al., 2001b; Germain, 2010).

Skin manifestations

Skin manifestations are an early and common feature of Fabry disease (Germain, 2010). The most common of these, angiokeratoma, are small, raised, reddish purple skin lesions that occur singly or in groups, most frequently on the trunk, limbs, umbilicus, and genitals, and

sometimes on other areas such as the head, face, and oral mucosa (Orteu et al., 2007; Germain, 2010). Angiokeratoma first appear in children between 5 and 13 years of age or older, and may increase in size and number with age (Sivley, 2013; Orteu et al., 2007; Germain, 2010). Other dermatological features include macular angiomas (similar to angiokeratoma but with little or no thickened skin), and telangiectasia (dilated vessels appearing as lines on the skin), peripheral oedema, and lymphedema (Orteu et al., 2007). In a review of 714 patients (48% male) with Fabry disease, skin manifestations were reported in 78% of males and 50% of females, and angiokeratoma in 66% of males and 36% of females (Orteu et al., 2007).

Respiratory symptoms

Respiratory symptoms, including dyspnoea, chronic cough, and wheezing, are common in patients with Fabry disease and worsen with age (Sivley, 2013; Germain, 2010). In a study of 50 patients (23 men), 84% showed abnormalities on respiratory function testing; mild to severe airway obstruction was reported in 61% of men and 26% of women (Magage et al., 2007).

Ocular symptoms

Corneal opacities are common and early manifestations of Fabry disease (Germain, 2010). The most distinctive feature is corneal verticillata, a whorl-shaped lesion on the cornea that occurs in virtually all patients by 10 years of age and even earlier in males with classic disease (Sivley, 2013). Other common features include lens cataracts, tortuosity of conjunctival and retinal vessels, and dry eye syndrome (Sivley, 2013; Germain, 2010). Corneal opacities and vessel tortuosity are generally not associated with visual symptoms (Germain, 2010).

Other manifestations

Other manifestations of Fabry disease can include:

- Osteopenia and osteoporosis, which have been associated with lumbar fractures (Germain et al., 2005; Germain, 2010)
- Auditory symptoms, including progressive sensorineural hearing loss, sudden deafness, and tinnitus (Sivley, 2013; Germain et al., 2002)
- Vestibular symptoms, including dizziness, and debilitating rotational vertigo (Sivley, 2013)
- Mild peripheral cytopenias; anaemia in particular is common (Sivley, 2013; Germain, 2010).

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

Fabry disease is a rare condition that occurs in people of all ethnic backgrounds (Orphanet, 2015; Germain, 2010). Accurate measures of disease prevalence have been difficult to

obtain, but estimates of 1 in 40,000 to 1 in 117,000 are frequently cited (Desnick et al., 2001; Meikle et al., 1999; Germain, 2010).

The theoretical prevalence of patients with symptomatic Fabry disease in England is estimated to be 1 in 64,600 (0.002%) based on a report by the Northern Genetics Service (Brennan and Parkes, 2014) (Section 13.1). Using the projected population estimate for England in 2016 of 55,218,701 (Office for National Statistics, 2015c), this equates to 855 patients with signs/symptoms of Fabry disease.

A diagnosis rate was derived from the number of patients enrolled in the Fabry Disease Registry and Fabry Outcome Survey compared to the theoretical prevalence, equating to 78.6%. Thus it is expected that there are 672 diagnosed patients in England.

Considering migalastat is expected to be used in line with the starting and cessation criteria for ERT, per treatment guidelines (Hughes et al., 2013a), a 60% treatment rate based on analyses of the Fabry Disease Registry is applied to the diagnosed population to estimate the number of patients who will receive treatment for Fabry disease. This is in line with clinical expert estimates of the current treated population (Amicus Therapeutics, 2016a). Of these patients:

- 30-50% have amenable mutations (Benjamin et al., 2009; Filoni et al., 2010; Germain et al., 2012; Shabbeer et al., 2006; Ishii et al., 2007; Wu et al., 2011).
- 97% of treated patients are aged 16 or over (based on longitudinal cohort study of people with lysosomal storage disorders in the UK) (Wyatt et al., 2012)
- 91% of treated patients do not have ESRD: average of a reported 83% for males and 99% for females, obtained from an analysis of UK Fabry Registry data (Mehta et al., 2004)

Based on the above and taking the midpoint of the percentage with amenable mutations, it is anticipated that there are currently 142 patients in England eligible for migalastat.

The full derivation of the number of patients who are eligible for migalastat is shown in Table B6.5. Please see Section 13.2 for further detail.

Table B6.5: Derivation of number of patients who are eligible for migalastat

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**

ESRD, end-stage renal disease

In a separate National Collaborative Study for Lysosomal Storage Disorders report, 499 patients with a confirmed diagnosis of Fabry disease in the UK are reported (Anderson et al., 2014). In addition, in interviews with clinical experts the diagnosis rate was reported to be as low as 50% (Amicus Therapeutics, 2016a), therefore the numbers in the above table may overestimate the number of diagnosed patients.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

In patients with Fabry disease, the accumulation of GL3, lyso-Gb3, and other glycosphingolipids in cells followed by secondary tissue-damaging processes lead to progressive organ damage and reduced life expectancy (Sivley, 2013; Germain, 2010).

Several studies have reported on mortality in patients with Fabry disease before the advent of ERT in 2001, as follows.

- In a study of 98 male patients, the median survival was 50 years, or about a 20-year reduction in survival compared to the general population, with a sharp decline in survival after age 35 (MacDermot et al., 2001b). The predominant causes of death were renal failure and stroke (MacDermot et al., 2001b).
- In a study of 60 female patients, the median survival was 70 years, or an approximate reduction in survival of 15 years compared to the general population, with a gradual decline in survival after approximately age 35 (MacDermot et al., 2001a). Twenty-eight percent of patients died of stroke (MacDermot et al., 2001a).
- In a retrospective review of 447 patients (62% male), the median survival in 20 male patients who died was about 59 years. The median age at first renal, cardiac, or stroke event or death was about 41 years in males and 53 years in females (Schiffmann et al., 2009).

A study based on the Fabry Outcome Survey reported mortality data for 1,453 patients with Fabry disease, most of whom had received ERT at some point during the course of their disease (Mehta et al., 2009). The mean age at death was 51.8 years in 43 male patients and 64.4 years in 7 female patients. Cardiac disease was the most common cause of death in both males and females. The next most frequent causes in males included renal disease, cerebrovascular disease, and infection. The study also included data on 181 affected relatives of survey patients, most of whom died before ERT became available. The primary cause of death in male affected relatives was renal disease, followed by cardiac disease and cerebrovascular disease. In female affected relatives, the primary causes were cerebrovascular disease and cardiac disease followed by malignancy and renal disease.

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

The clinical profile of Fabry disease results in a substantial burden for patients and their families. Patients with Fabry disease suffer from a considerably worse quality of life compared to healthy individuals (Arends et al., 2015).

Because the symptoms are often nonspecific and variable, a diagnosis often is not made until the disease has progressed for years or decades, at which point organ damage has already occurred (Germain, 2010). Multiple studies have shown that it can take 15 years or longer for Fabry disease to be diagnosed (Mehta et al., 2004; Wilcox et al., 2008; Martins et al., 2013). Patients often consult multiple healthcare providers over many years in an effort to determine the cause of their symptoms (Mahmud, 2014), which has a detrimental impact on quality of life and economic consequences.

Patients with Fabry disease are faced with a lifelong, incurable, debilitating, progressive disease. The symptoms affect multiple body systems and have an early onset, resulting in a substantial quality of life burden and economic cost (El-Abassi et al., 2014; Eng et al., 2006; Guest et al., 2010, 2011). The physical and psychological consequences of Fabry disease affect nearly all aspects of daily living and result in decreased quality of life (Wilcox et al., 2008; Löhle et al., 2015; Wagner et al., 2014; Żuraw et al., 2011; Bouwman et al., 2011; Morier et al., 2010; Hopkin et al., 2008; Muller, 2006).

The impact of symptoms of Fabry disease on quality of life is discussed in Section 10. Pain is the most significant, debilitating contributor to diminished quality of life in Fabry disease patients (Miners et al., 2002; Cole et al., 2007). Anhidrosis (abnormal lack of sweat in response to heat) is associated with a significant decrement in physical function, general health and vitality (Gold et al., 2002). Gastrointestinal symptoms are a prominent and clinically important manifestation of Fabry disease. Patients commonly suffer from debilitating gastrointestinal symptoms, including diarrhoea, nausea, faecal incontinence, vomiting, abdominal pain, and constipation (Banikazemi et al., 2005; Hoffmann et al., 2007). Results from 366 male and female patients with Fabry disease in the Fabry Outcomes Survey revealed that gastrointestinal symptoms were reported in 55% of males and 50% of females (Mehta et al., 2004). Gastrointestinal manifestations of Fabry disease often have profound negative effects on social and economic functioning and quality of life in male and female patients (Gold et al., 2002). Thus, improving gastrointestinal symptoms is clinically relevant in the daily life of patients with Fabry disease. Chronic fatigue also has a significant impact on patients lives (see box below).

UK Fabry Patient Survey (2016)

Amicus Therapeutics have, in collaboration with the MPS Society, undertaken interviews to better understand Fabry disease and its impact on the lives of patients and families. Although the number completed to date is relatively small (n=8) the feedback consistently

demonstrates the significant impact Fabry disease has on patients' lives (also see section 7.2).

Patients described severe pain (hands and feet), chronic fatigue, GI events and heat intolerance, with symptoms making normal life impossible:

- "I have pain and fatigue which means I cannot work. I spend most of my time managing my pain". "In the morning takes 2- 3 hours to get up due to pain and tiredness, afternoon I generally need to sleep and pain is manageable .... I have a lot of problem controlling my temperature and this increases the pain in my body generally more intensified in hands feet and shoulders". The worst symptom was pain which can "can go on for as long as 24 hours …I can't make it better"
- "Getting out of bed is a struggle and day to day I feel very restricted because of my symptoms - Life on a daily basis is a challenge, I only feel able to deal with everything a couple of days a month when I have more energy"
- "I can't plan anything … on a bad day have intense pain, feel down and moody, and generally have to sleep"

Coping with symptoms of Fabry disease affected patients' ability to work, carry out day to day activities and participate in hobbies or social engagements:

- "I have pain and fatigue which means I cannot work"
- "I suffer with the cold, I struggle to wash my hair as I have restricted movement in my shoulders" "I can't work full-time and have had to go part-time"
- "Fabry disease makes it difficult for me to lead a normal life [redacted] "I can only walk a short distance before the pain increases. I use a wheelchair on days out" "my mother has to help me with all self care when the pain is particularly bad which is 2-3 days a week" "I had to give up work full-time and trying to find part-time work" [redacted]
- "I am not able to plan anything and have had to give up work as I cannot predict when I will have a good day" "outside I can only walk about 50 metres before I have to stop and rest due to the pain"

Visiting family was more difficult where multiple family members were affected:

- "I haven't been to see my mother for about a year or my sister for two years as they live in other parts of the country and I can't travel far. [redacted]

[redacted]

- "Life is very restricted now"

Patients reported that going on holiday was difficult or not possible due to their symptoms:

- "I suffer when I go anywhere hot so have to stay in the shade when I go on holiday with the family. Travel insurance is also expensive"
- "I have never been abroad and the pain increases in the heat and the cold so generally I don't go away because I never know how I am going to feel."

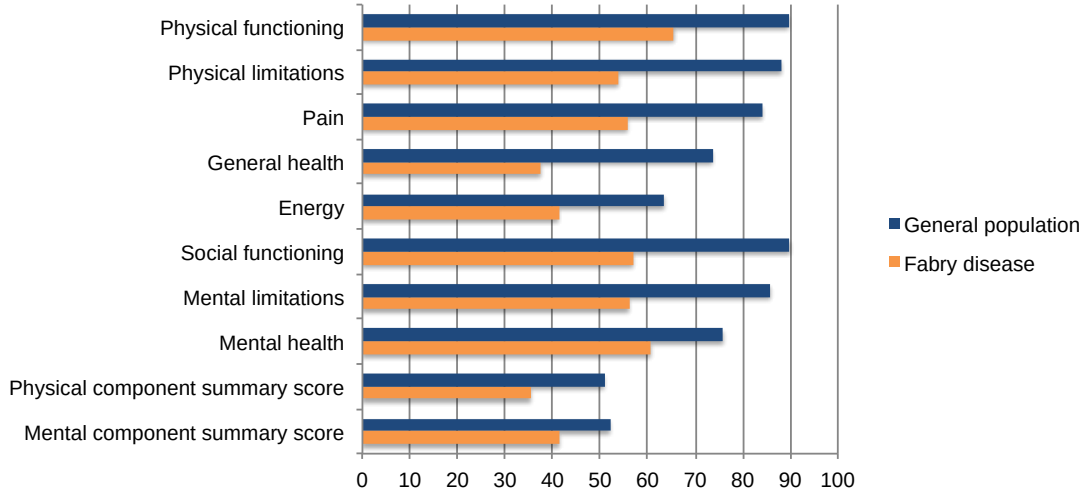
Patients consistently reported feeling social isolation, including feeling withdrawn and irritable due to their symptoms. Living with the symptoms makes patients “depressed, frustrated and angry”. “I will not engage with people as I become angry easily and feel it is better to be on my own”

Patients often stated that the unpredictability of symptoms can make it hard to plan and that they have to “take each day at a time”. “Life on a daily basis is a challenge, I only feel able to deal with everything a couple of days a month when I have more energy”.

Two patients reported relatively mild symptoms and that Fabry disease had little impact on their daily lives.

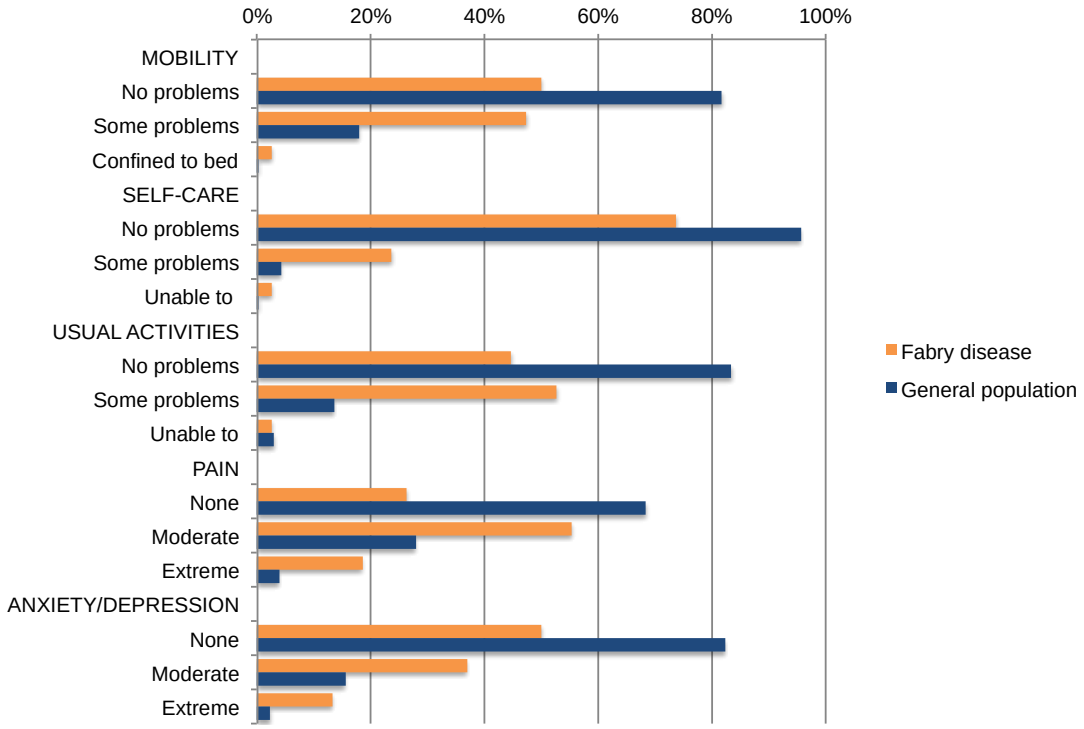
In a sample of 38 patients from the Fabry disease register in the UK prior to the introduction of ERT, Fabry disease was shown to consistently impact on every domain of the SF-36 and EQ-5D, resulting in significantly impaired physical and social functioning compared to the general population (Figure B7.1 and Figure B7.2, respectively) (Miners et al., 2002). This analysis is consistent with many other published studies in which patients with Fabry disease have been shown to have quality of life scores worse than those of the general population and comparable to or worse than those of patients with other chronic diseases (Table B7.1). This has been confirmed in a recent meta-analysis where patients with Fabry disease scored worse across all domains compared to the general population (Arends et al., 2015).

Figure B7.1: Quality of life scores of UK Fabry patients (untreated) compared to the general population using the SF-36 questionnaire



Source: (Miners et al., 2002)

Figure B7.2: Distribution of UK Fabry disease patients across the domains of the EQ-5D-3L compared to the general population



Source: (Miners et al., 2002)

Table B7.1: Studies of quality of life in Fabry disease

Study	Description	Results
(Löhle et al., 2015)	110 patients (50 males [88% receiving ERT], 60 females [60% receiving ERT]) >17 years (mean age 49 years attending a UK clinic and 57 matched controls were evaluated for motor and non-motor function and HRQL	• Patients with Fabry disease had worse scores on the SF-36 and EQ-5D and greater pain severity and interference on the BPI, as well as more daytime sleepiness and depressive symptoms, than controls
(Wagner et al., 2014)	96 patients (45 males, 51 females) >16 years (mean age 40 years) and naïve to ERT who attended a German clinic were evaluated with the SF-36	• When stratified by kidney function, patients requiring dialysis had significantly worse scores on the MCS • Worse PCS scores were found in patients with moderate (eGFR < 60 mL/min) or greater kidney dysfunction • The primary factors associated with worse scores on the PCS were need of renal replacement therapy, pain, and CKD
(Żuraw et al., 2011)	HRQL was evaluated in 33 patients (20 males [all receiving ERT], 13 females [none receiving ERT]) >7 years (mean age 31 years) attending a Polish clinic	• SF-36 scores were significantly worse for patients with Fabry disease compared to Swedish normative data • On the EQ-VAS, patients with Fabry disease had a significantly worse

Study	Description	Results
		subjective perception of health status compared to a matched Polish cohort • EQ-5D and EQ-VAS scores were numerically worse for male vs. female patients, while SF-36 general health perception scores were worse for female patients vs. male patients • In patients who received ERT, a decrease in burning extremity pain, GI disorders, and skin lesions were the most important HRQL symptoms improved by ERT
(Bouwman et al., 2011)	26 patients (9 males and 19 females) aged 18 to 35 years attending the Netherlands national expertise centre were evaluated clinically and with the SF-36 for HRQL and the CoL for psychosocial development	• Men with Fabry disease had significantly worse SF-36 scores than the general population in the domains of physical functioning and pain • Women with Fabry disease had significantly worse SF-36 scores than the general population in the health perception domain
(Morier et al., 2010)	23 patients (8 males, 15 females) aged 7 to 55 years from a single family in the US were evaluated for visual dysfunction and HRQL	• 13% of both male and female patients felt that Fabry disease had greatly affected their lives; another 33% of male patients and 38% of female patients felt that it had somewhat affected their lives
(Hopkin et al., 2008)	36 paediatric patients (10 males, 26 females) <18 years from the Fabry Registry were evaluated for HRQL	• Male patients ≥14 to <18 years reported significant worse SF-36 scores in 7/8 domains (all except role emotional) than males ≥18 to <25 years in the general population, and female patients ≥14 to <18 years reported significant worse SF-36 scores in 2/8 domains (bodily pain and general health) than females ≥18 to <25 years in the general population
(Wilcox et al., 2008)	368 female and 190 male patients ≥18 years from the Fabry Registry were assessed for pain with the BPI and for HRQL with the SF-36	• Scores for both male and female patients with Fabry disease were below norms for the general population by age 35, but scores of male patients began to decline earlier than those of female patients
(Low et al., 2007)	22 patients (20 males, 2 females) >16 years (mean age 40 years) attending an Australian clinic were evaluated for neurologic function and HRQL	• SF-36 and EQ-5D scores were significantly worse than those in the general population • In the 16 patients receiving ERT, scores did not improve during 21 months of ERT; in the 10 patients who had received a total of 81 months of ERT, the only SF-36 score to significantly improve was bodily pain
(Vedder et al., 2007a)	Assessment of HRQL using the SF-36 and assessment of pain using the BPI in 96 untreated adults who visited a medical centre in Amsterdam	• Both male and female patients reported a lower quality of life compared with healthy individuals • A tendency towards a higher quality of life was seen in the males (p=0.053)

Study	Description	Results
	between 1999 and 2005.	• No difference in BPI score (pain at its worst) between male and female patients could be detected (p=0.28)
(Wang et al., 2007)	44 female patients (mean age 46 years) from a US centre were evaluated with the SF-36 and for pain on the BPI	• Mean SF-36 scores for patients with Fabry disease on both the physical and mental components were below norms for the general female population • Scores for Fabry disease patients on a scale measuring pain levels indicated that pain affected their mood, ability to work, enjoyment of life, and general activity
(Street et al., 2006)	SF-36 scores of 202 female US participants in FSIG (mean and median age 35 to 44) were compared to those of healthy women (n=16,608 from the Women's Health Study), men and women with MS (n=179), and men and women with RA (n=679)	• Women with Fabry disease scored significantly worse than healthy women on all domains of the SF-36 • The scores of the women with Fabry disease were clinically similar to those of patients with MS and RA
(Faggiano et al., 2006)	18 patients (9 males, 9 females) aged 21 to 64 years were evaluated for endocrine function and HRQL and compared with 18 age- and sex-matched controls	• SF-36 scores were significantly worse for patients with Fabry disease compared with controls in all domains • The scores of patients who were receiving ERT (n=10) were improved vs. those of patients not receiving ERT, but still worse than controls
(Ries et al., 2005)	Quality of life was evaluated with the CHQ in 25 male paediatric patients (mean age 12 years) attending a US centre	• Compared with age- and sex-matched controls, male patients with Fabry disease had worse scores on the CHQ, with significantly worse scores for bodily pain and mental health • Pain scores were similar to those of children with juvenile RA
(Gupta et al., 2005)	Assessment of pain using the BPI questionnaire in 52 untreated adult women with Fabry (mean age 43.3 years) attending a single US centre	• Responses to the BPI questionnaire (scale of 0-10, 10 being worst) demonstrated a wide range of pain severity and pain interference • Mean pain severity score was 2.8 (SD 2.23; range 0.0-7.0) • Mean % relief from medications was 48 (SD 38.7; range 0.0-100.0) • Mean pain interference score 2.8 (SD 2.7; range 0.0-8.7)
(Gold et al., 2002)	SF-36 scores for 53 male patients (17% aged <20 years, 26% aged 20 to 40 years, 57% aged >40 years) responding to a survey from FSIG were compared with those for patients with AIDS, ESRD, Gaucher disease, and stroke	• SF-36 scores for patients with Fabry disease were: ○ worse in all domains than those for patients with Gaucher disease or stroke ○ worse than those for patients with ESRD except in physical function

Study	Description	Results
	from the literature	○ most similar to those of patients with AIDS • Factors that were associated with worse SF-36 scores in patients with Fabry disease included having a stroke, heart disease, kidney disease, neuropathic pain and other pain, and anhidrosis
(Miners et al., 2002)	SF-36 and EuroQoL questionnaire data for 38 male patients (mean age 37 years) in a UK registry were compared to scores in the general population and to those for men with severe haemophilia from national data sets	• After adjusting for age differences, men with Fabry disease had significantly worse scores on the SF-36 and EuroQoL than either the general population or men with haemophilia
(MacDermot et al., 2001b)	Assessment of neuropathic pain by the McGill pain questionnaire in a cross-sectional patient cohort from the UK Fabry disease clinical and genetic register (98 males, mean age 34.8 years)	• Neuropathic pain was present in 77% (n=93) • The majority developed pain in the median age range of 4-12 • 77% of patients experienced pain at their present age, range 4-61 years • A total of 29.2% of respondents described their pain as a constant background pain whereas 53.6% described their pain as both constant background pain coupled with attacks of excruciating pain occurring on average four to six times per year and lasting several days • The median pain score in all patients, even those on anticonvulsants, was 5 (on scale 0-10). Over half (65%) scored between 5 and 9, which is considered as pain severity interfering with daily living. • In 11% of patients the pain has stopped, at a mean age of 24 years, age range 12-35 • A total of 12.9% (12 patients) had never had neuropathic pain

AIDS=acquired immunodeficiency syndrome; BPI=brief pain inventory; CHQ=Child Health Questionnaire; CKD=chronic kidney disease; CoL=Course of Life questionnaire; EQ-5D=European Quality of Life-5 Dimensions; EQ-VAS=European Quality of Life Visual Analogue Scale; ERT=enzyme replacement therapy; ESRD=end-stage renal disease; EuroQoL=European Quality of Life; FSIG=Fabry Support and Information Group; GI=gastrointestinal; HRQL=health-related quality of life; MCS=mental component summary; MS=multiple sclerosis; QOL=quality of life; PCS=physical component summary; RA=rheumatoid arthritis; SF-36=Short Form-36 Health Survey.

Psychiatric disorders and social problems have also been noted in patients with Fabry disease (Sivley, 2013; Germain, 2010). In the largest survey of psychiatric disorders in patients with Fabry disease (184 of 296 patients responding), responses consistent with clinically significant depression were reported by 46%, including 28% with severe clinical depression (Cole et al., 2007). Similarly, in a smaller study, 58% of 30 patients had scores indicating depression whilst 39% had scores consistent with borderline or full blown

generalised anxiety disorder (Laney et al., 2010) and in another, 63% of 16 patients had depressive symptoms (Segal et al., 2010). It is thought likely that depression is a reaction to the symptoms of Fabry disease, rather than a symptom of the disease itself (Bolsover et al., 2013). Depression has been shown to seriously impact quality of life in patients with Fabry disease, using a variety of questionnaires including the SF-36, EuroQoL and MMPI-2 (Miners et al., 2002; Gold et al., 2002; Street et al., 2006).

In addition, there are some limited data that Fabry disease can affect aspects of cognitive function. A meta-analysis suggested that executive function, information processing speed, and attention may be impaired in patients with Fabry disease (Bolsover et al., 2013).

Furthermore, because the pervasive, severe symptoms of Fabry disease can affect all aspects of daily life, it is thought that they can impair social-adaptive functioning, leading to issues in social interactions, school attendance, sports participation, and employment opportunities (Sivley, 2013; Laney et al., 2010). Deficits in social functioning such as reduced participation in school, sports, social activities, and employment have been found in both male and female patients with Fabry disease (MacDermot et al., 2001b, 2001a; Laney et al., 2010). For example, in a study of 16 paediatric patients, over the course of 12 weeks, patients missed 12% of school days, and had difficulty performing low-energy activities (e.g., dressing, eating, getting out of bed) on 12% of days, moderate-energy activities (e.g., climbing stairs, walking to school) on 18% of days, and high-energy activities (e.g., running) on 29% of days (Wraith et al., 2008).

Fabry disease also affects employment and productivity. A cross-sectional study based on 98 men in the UK Fabry disease registry found that just over half were employed, even though most patients were in their thirties (MacDermot et al., 2001b). Seventy percent reported that pain interfered with their ability to work, and about the same number reported that other symptoms of Fabry disease such as fatigue or diarrhoea interfered with their ability to work. This study was performed before ERT became available. In another study including males and females in which the majority of patients (65%, N=184, mean age 44 years) were receiving ERT, only 59% were employed (Cole et al., 2007). In this study, approximately 16% noted that they were unemployed due to sickness or disability, which was significantly higher than in the national population (4%). A more recent study compared 28 young adults (median age of males 25 and females 27) with Fabry disease, most of whom (64%) were being treated with ERT, to a matched control group and found no significant difference in employment rates between the 2 groups (Fabry versus control: employed 71% versus 76%) (Bouwman et al., 2011).

The quality of life impact of Fabry disease goes far beyond the impact on the patient. Family members and other informal caregivers are involved in the care of patients as well as the management of their disease, which requires a skilled multidisciplinary team, and careful, individualised decision-making with close consultation among the patient, physicians, family members, and other caregivers (Eng et al., 2006; Biegstraaten et al., 2015; Wang et al., 2011; Laney et al., 2013). The quality of life impact is therefore expected to be particularly severe in households with more than one patient with Fabry disease. Women who care for male relatives with Fabry disease may often be drained physically and emotionally from daily caregiving responsibilities (Street et al., 2006). Caring for a person with extensive medical issues has been shown to have a negative effect on the quality of life of the caregiver and increases the risk for depression (Alvarez-Ude et al., 2004).

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

While ERT is effective in many patients, it does not fully address the therapeutic need in Fabry disease. The biweekly IV infusions of ERT can interfere with the lives of patients and their caregivers, and are associated with a risk of infusion-associated reactions and infections (Ramaswami, 2011; Cousins et al., 2008; Milligan et al., 2006; Borgwardt et al., 2013; Parini et al., 2010). As an oral treatment, migalastat does not cause infusion-associated reactions and offers a more convenient alternative to ERT that will not interfere with the daily lives of patients. In addition, there is negligible risk of immunogenicity with migalastat because it is a small molecule, which means that there is no need for dosing adjustments in relation to formation of antibodies.

Amicus Therapeutics sponsored an international survey of people living with Fabry disease and parent/guardians of those under age 18 in the UK, Canada, and the US to better understand the burden of treatment with the existing ERTs and the effect on these patients' lives (the "Fabry Infusion Survey".) The survey was administered through Fabry patient advocacy organisations, so respondents were not aware of Amicus' sponsorship of the survey. The objective of the Fabry Infusion Survey was to gather information on the treatment experience of patients with Fabry disease. Among patients who have received ERT, the goal was to assess the effect of ERT on their lives. For patients who were not receiving ERT, the goal was to determine the reasons why they were not receiving therapy. Only the methods and results of the UK survey are reported here, as they are the most relevant for the NICE appraisal of migalastat. The results from Canada and the US were similar.

A clinical team at Amicus developed the 53-question survey instrument. The Fabry Patient Advisory Board of Amicus reviewed it for content and took the survey as the survey pilot. The survey was also reviewed by UK Society for Mucopolysaccharide Diseases Society (UKMPS Society) Chief Executive, Christine Lavery and Engage Health Inc. The survey was conducted with patients with Fabry disease ≥18 years old and with the parents or caregivers of patients <18 years old. In the UK, patients were recruited from members of the UKMPS Society. The organisation was paid an honorarium for sharing the survey with their membership. Surveys from the UKMPS Society were entered online by a registered nurse based on face-to-face interviews with patients. A separate survey was completed for each family member with Fabry disease. Respondents received a gift card (£38 equivalent) per completed survey.

From the UK Fabry Infusion Survey, a total of 107 surveys were conducted between November 17, 2014, and December 11, 2014. A total of 6 records were removed from the analysis (2 did not provide authorisation, 2 were duplicates, and 2 were test surveys). Thus, a total of 101 records were used in the analysis.

Exact locations of the respondents were not reported but the distribution of respondents can be approximated from questions regarding the healthcare provision, of which 66/80 of adult

patients with Fabry disease answered completely. Fifty-five of the 66 accessed care provided through NHS England, 3 NHS Scotland, 2 NHS Northern Ireland, 5 NHS Wales and one from Jersey.

Any data discrepancies were addressed using the following strategies:

- When a number was expressed as a range, the mean was used.
- Any answer provided as “I don’t know” or “not sure” was deleted as if the person did not answer the question.
- For any person who selected “no” when asked if they had interruptions in therapy, their “no” was corrected to a “yes” if they provided a positive number to subsequent questions regarding number of interruptions and number of infusions missed.
- For number of family members diagnosed, if the person noted “unknown”, it was deleted and left as if they did not respond.

Results were generated in *Excel* using the “sort” function to tabulate total number of respondents and then determine percentages. Other descriptive statistics (such as mean, median, mode) were calculated in the *Statistics Package for the Social Sciences* (IBM SPSS Statistics 19). The Wilcoxon test was used in SPSS to test for any statistically significant differences in infusion time between males and females, with alpha set at 5%. The results of the Fabry Infusion Survey are detailed in Table B7.2.

Limitations for this survey include potential variations in data based on several different modes of collection (online or paper by patient, online by interviewer), convenience sampling, and the self-selection of patients to complete the survey.

Table B7.2: Results of the Fabry Infusion Survey (UK)

Infusion time
Infusion-related reactions

[redacted]

Effect of ERT on employment

[redacted]

Effect of ERT on daily life

[redacted]

[redacted]

Interruptions in Infusion Therapy

[redacted]

[redacted]

In the recent UK Fabry Disease Patient Survey (2016) described above, patients consistently cited that they would prefer not to have bi-weekly infusions and their associated burden, as well as more convenient access to specialist care:

- “I would like to be able to have a tablet form of treatment as the ERT is very restrictive. I would like not to have the drug fridge”
- “It would be easier if treatments could be non-invasive and checkups more local” “it is difficult to find a vein each time (for infusion) and having to set aside two hours this is a constant bind”
- “I would like not to have to travel so far to see my specialist, be able to take a pill rather than having infusion …Not to have the fridge for my drugs as I have limited space, and it reminds me every day I have Fabry” “I can’t work for a day due to the ERT treatment and having to take time off to go for hospital appointments”
- “I would prefer not to have two weekly infusions and want them longer or an alternative to ERT. I would prefer to have a local hospital so I don’t have to travel so far to see the specialist” “Being tied to a fortnightly infusion, being cannulated, restricts how long I can go on holiday for” “would prefer if I didn’t have to be cannulated, could have it less often and not have to store the drug”
- “I would like not to have to be restricted by a fortnightly infusion, not to have to wait for drug delivery and have to store it. When I did work, it was difficult to take time off for the infusions. I tend to go to bed after treatment so generally a whole day has been disrupted. I would like it to be a longer period in between treatments but I know that is not practical”

As an oral treatment, migalastat offers a more convenient alternative to ERT that will avoid loss of productivity from ERT infusions and will benefit patients that have to miss work due to infusions or are unable to perform daily activities or work following their infusions. Patients having to miss infusions due to travel would also benefit from an oral treatment such as migalastat. As an oral treatment, migalastat is not associated with IARs that patients may wish to avoid. Furthermore, patients receiving migalastat do need to receive the

premedication used to prevent IARs. [redacted]

In the UK Fabry Disease Patient Survey (2016) feedback from patients receiving migalastat (n=3), in contrast to those reciving ERT, was that it is an easy and convenient treatment:

- "I am happy with my treatment regime taking AT1001 (migalastat) is easy and convenient far less restrictive than ERT… it has made life so much easier and I can't think of anything negative to say about it". "I can get on with life and forget about the fact that I have fabry disease. I can go away for long holidays [redacted] "[the benefits are] amazing. No ties to treatment regime, no worries about not being able to get a vien, no storage problems or waiting for deliveries. My heart condition is improving. It is a win win situation" "My family feel the same way as they have seen the burden of having ERT and the constraints."
- "[Migalastat is] easy, simple, no fridge required, no need for a nurse and I'm able to go on holiday when I want." "Has made my work and social life better, no worries about infusion day".

Caregivers also experience the burden experienced by patients in terms of inconvenience and time away from other responsibilities. Migalastat has a once-every-other day oral administration regimen that does not interfere with the lives of patients or caregivers. Furthermore, treatment can be kept private, which is expected to be of importance to some patient groups such as university students.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

NHS England and Department of Health Policy

There is no NICE guidance or NICE Pathways for Fabry disease. The following NHS England (NHSE) and Department of Health policy guidance exists:

1) NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. Available at: *http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf*

Lysosomal storage disorder (LSD) services include services provided by Highly Specialist LSD Centres including outreach when delivered as part of a provider network. This applies to provision in adults and children. Other relevant services described in the NHSE Manual for

prescribed specialised services include Highly Specialist Metabolic Disorder services (all ages).

The prescribed specialised services document describes LSDs as a group of rare genetic storage disorders, characterised by specific lysosomal enzyme deficiencies. There are seven LSDs included in the prescribed specialised services:

- Anderson-Fabry's disease (Fabry disease)
- Gaucher's disease
- Mucopolysaccharidosis type I (MPSI, which occurs as Hurler‟s syndrome, Hurler-Scheie syndrome and Scheie syndrome)
- Mucopolysaccharidosis type VI (MPSVI or Maroteaux Lamy syndrome)
- Pompe disease
- Mucopolysaccharidosis type II (MPSII)
- Niemann Pick type C

The service has a caseload of about 1,800 patients. NHS England commissions services for adults and children with lysosomal storage disorders from the following designated Highly Specialist Lysosomal Storage Disorder Centres:

- Birmingham Children's Hospital NHS Foundation Trust
- Cambridge University Hospitals NHS Foundation Trust (adults)
- Central Manchester University Hospitals NHS Foundation Trust (children) Great Ormond Street Hospital for Children NHS Foundation Trust
- Royal Free London NHS Foundation Trust (adults)
- Salford Royal NHS Foundation Trust (adults)
- University College London Hospitals NHS Foundation Trust (adults and children)
- University Hospitals Birmingham NHS Foundation Trust (adults)

The prescribed specialised services document states that LSDs can be treated using ERTs or substrate reduction therapy (SRT) and that there are licensed ERTs or SRTs for seven LSDs.

NHS England currently commissions the following drugs/devices:

- Agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme) for Fabry disease
- Other drugs for other conditions include:
    - Laronidase (Aldurazyme)
    - Imiglucerase (Cerezyme, Vpriv)
    - Iduronase (Elaprase)
    - Aglucosidase alfa (Myozyme)
    - Galsulfase (Naglazyme)
    - Miglustat (Zavesca)

Some of these therapies are provided through home care mechanisms which includes agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme) which are administered intravenously in the patient's home by a nurse or by themselves.

2) NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. Available at: *https://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf*

This service specification for children concentrates on the disorders that are currently managed by ERT or SRT. Haematopoietic stem cell therapy (HSCT) for LSD is excluded from this specification.

3) NHS England Standard Contract for Metabolic Disorders (Adult), 2013. Available at: *http://www.england.nhs.uk/wpcontent/uploads/2013/06/e06-metab-disordersadult.pdf*

The standard contract for Metabolic Disorders describe the service aims regarding identifying and diagnosing patients who are suspected of having an Inherited Metabolic Disease (IMD), improving life expectancy and quality of life for adults affected by one of the IMDs detailed in the document – this includes Fabry disease.

The objectives of the specialised adult IMD centres is to provide:

- 24/7 access to clinical advice in conjunction with other adult and paediatric centres in an agreed service provider network
- High-quality clinical expertise in accordance with national policy and guidance where available or in agreement with accepted clinical practice to:
    - Provide timely diagnosis with appropriate counselling and psychological support to the patient and family/carers
    - Provide dedicated IMD inpatient and outpatient facilities
    - Provide high quality proactive diet and/or drug treatment and care
    - Agree and monitor compliance of care pathways and treatment protocols (elective and emergency)
    - Ensure smooth transition from paediatric to adult care
    - Ensure equity of access to services for the IMD population
- In-house training and education for IMD physicians completing Royal College of Physicians and Royal College of Pathology metabolic training programme
- Provide expert advice and education to primary, secondary and tertiary care provider units under agreed shared care arrangements where clinically appropriate, and to professionals of other specialised services, e.g. nephrology, cardiology, neurology, linked to IMD conditions
- Provide expert advice to non-medical professionals, including local authorities and the voluntary sector, to facilitate holistic care for IMD patients and support to their families/carers.

4) Department of Health rare diseases strategy, November 2013. Available at: *https://www.gov.uk/government/publications/rare-diseases-strategy*

This Strategy is an overarching framework document that sets out a shared vision for improving the lives of all those with rare diseases. The focus throughout is patients and families.

It states there are 5 areas where all 4 countries of the UK will take action, either together or individually:

- Empowering those affected by rare diseases
- Identifying and preventing rare diseases
- Diagnosis and early intervention
- Coordination of care
- The role of research

Adult Fabry Disease Standard Operating Procedures (England)

These standard operating procedures (SOPs) were prepared in 2012 by a group of prescribing physicians working in designated treatment centres at the invitation of the National Specialist Commissioning team (Hughes et al., 2013a). The SOP provides an update to previous UK guidelines (Hughes and Ramaswami, 2005) and are followed by clinicians in England (Amicus Therapeutics, 2016a).

The SOPs describe the clinical features, diagnosis, treatment and monitoring of Fabry patients, including assessment of treatment response and start/stop criteria (see Section 8.2)

European Fabry Working Group Consensus Statement

The 2015 European Fabry Working Group Delphi consensus panel statement, generated by 28 experts in the treatment of Fabry disease, provides international consensus guidelines on starting and stopping ERT (see Table B8.2) (Biegstraaten et al., 2015). It should be noted that clinicians in England indicated they follow the English SOPs (above).

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

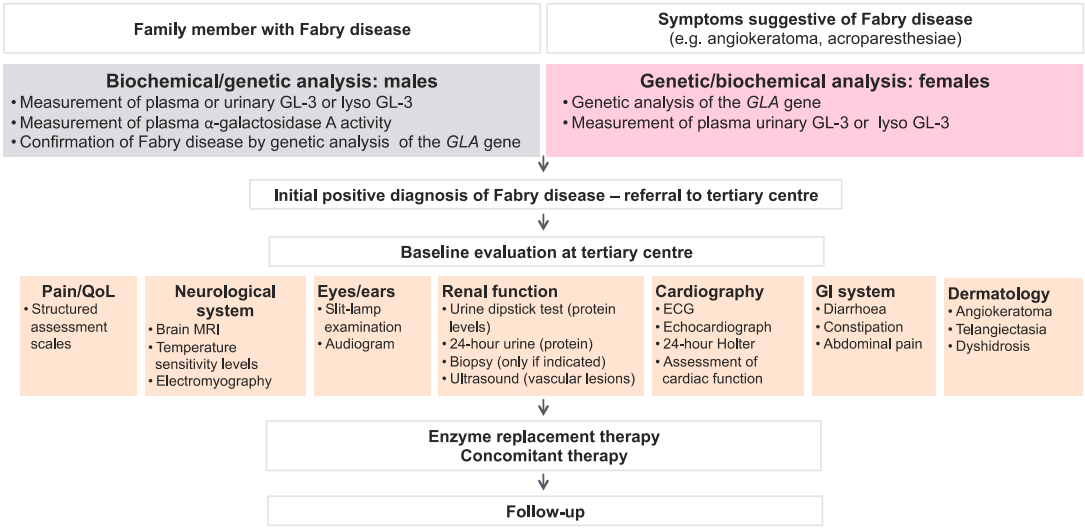
Diagnostic process

A general diagnostic algorithm with appropriate investigations according to organ system involvement is shown in Figure B8.1. If clinical examination raises a suspicion of Fabry disease, biochemical and/or genetic confirmation is needed. Assay of the α-galactosidase A activity in leukocytes or dried blood spots will usually confirm the diagnosis in males. Plasma or urinary GL3 has also been used in the biochemical diagnosis of Fabry disease, but in females the level of GL3 is generally lower than in males, and is not elevated in some patients with particular mutations in the GLA gene. In female heterozygotes, α-galactosidase activity is often within the normal range. Diagnostic confirmation should therefore be made by genetic analysis in suspected cases (Hughes et al., 2013a). A diagnosis of Fabry disease is only confirmed where a mutation previously documented as causing relevant pathology is identified. If a new mutation/sequence variant is identified this should be accompanied by biochemical evidence of decreased enzyme activity in males (decreased in expression

systems in females) and evidence of substrate accumulation in urine or on biopsy (Hughes et al., 2013a).

Family screening, including a pedigree analysis, is carried out for each new presenting patient (following consent).

Figure B8.1: Diagnosis and assessment of patients with Fabry disease



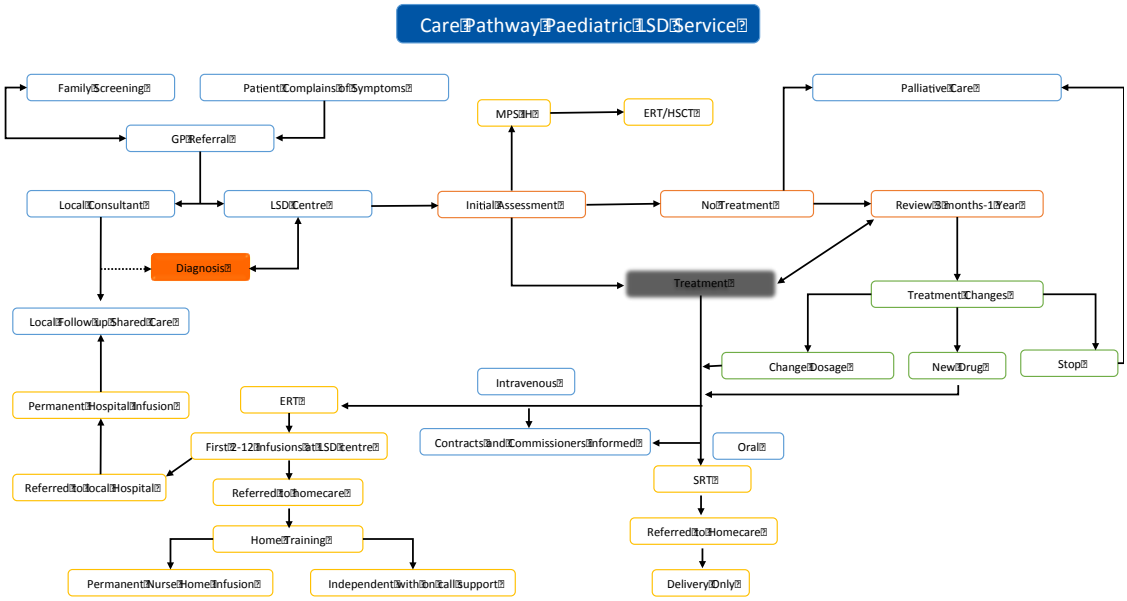
Source: (Mehta et al., 2010a; Hughes et al., 2013a)

Care Pathway

The majority of new index cases of Fabry disease are identified by Cardiologists or Nephrologists and referred onto specialist centres for baseline assessment and ongoing management, according to the Adult Fabry Disease Standard Operating Procedures and UK guidelines (Hughes et al., 2013a; Hughes and Ramaswami, 2005). Many patients are diagnosed via family screening (Amicus Therapeutics, 2016a). The following care pathway (Figure B8.2) is described in the NHS standard contract for LSD service (children). Whilst a similar diagram is not described in NHS standard contract for metabolic disorders for adults (which includes LSDs) it is understood that a similar pathway applies.

Clinical experts in England stated that they review their adult patients with Fabry disease on an annual basis if not receiving ERT and 6-monthly when on ERT (Amicus Therapeutics, 2016a). This is in line with national guidelines (Hughes et al., 2013a).

Figure B8.2: Care Pathway for Paediatric LSD Service



Source: (NHSE, 2013)

Overview of current treatment

Overall, management of Fabry disease requires a skilled multidisciplinary team, and careful, individualised decision-making with close consultation among the patient, physicians, family members, and other caregivers. To date, only symptomatic therapies and ERT have been available for the treatment of diagnosed Fabry disease. Genetic counselling also plays an important role in informing patients and patient-relevant aspects of disease management, including psychosocial factors and HRQL (Eng et al., 2006; Biegstraaten et al., 2015; Hughes and Ramaswami, 2005; Laney et al., 2013). Thus, the available guidelines and expert opinions published worldwide currently address only these approaches.

Enzyme replacement therapy (ERT)

Currently, treatment for Fabry disease consists of ERT with recombinant human α-Gal A, administered via infusion every 2 weeks. Two products are available in the UK:

- Agalsidase alfa (Relagal); Shire Human Genetic Therapies AB
- Agalsidase beta (Fabrazyme); Genzyme Europe BV/Genzyme Corporation

The two drugs differ mainly in the cell line used for production, while agalsidase beta is produced in Chinese Hamster Ovary (CHO) cells, agalsidase alfa is produced in a human cell line, however biochemical studies have shown no functional difference between the 2 protein preparations (Genzyme Therapeutics, 2014; Shire, 2006; Lee et al., 2003).

An overview of both drugs, including indication and dosing, is provided in Table B8.1. In clinical trials both preparations have been shown to be broadly equivalent in the doses used as measured by laboratory assessment of treated versus placebo groups (e.g. statistically significant reductions in urine and plasma GL3 content, renal histology) (Hughes and Ramaswami, 2005). As such, UK guidelines do not recommend a particular ERT and assume that patients will be offered the choice of products (Hughes et al., 2013a).

Recommendations on initiation of ERT are based on establishment of diagnosis and presence of signs and symptoms (see Table B8.2). The benefits of early initiation of disease-modifying treatment are frequently emphasised (Eng et al., 2006; Biegstraaten et al., 2015; Hughes and Ramaswami, 2005; Burlina et al., 2011; Laney et al., 2013). Regular follow-up visits every 6 to 12 months are critical to assess response to treatment across organ systems and to adjust disease management strategies.

A number of guidelines are available that provide recommendations on when patients with Fabry disease should start therapy, based on disease subtype and the severity of presenting symptoms. They emphasise that:

- It is important that patients receive appropriate therapy in order to prevent further progression of Fabry disease that can lead to irreversible and costly cardiomyopathy, renal failure, and stroke.
- The aim of treatment is to prevent progression and where disease is already manifest to try to reverse or stabilise disease.
- ERT is less effective when started after the development of tissue fibrosis.

Initial ERT infusions are carried out under specialist supervision. In England, once tolerance is established, the majority of patients receive ERT in the homecare setting (Amicus Therapeutics, 2016a).

Table B8.1: Overview of agalsidase alfa and agalsidase beta

	Agalsidase alfa (Replagal)	Agalsidase beta (Fabrazyme)
Manufacturer/Distributor	Shire Human Genetic Therapies AB	Genzyme Europe BV/Genzyme Corporation
Marketing authorisation	First authorised in the EU in 2001 US application withdrawn in 2012	First authorised in the EU in 2001 First approved in the US in 2003
Indications for use	For long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-Gal A deficiency)	For long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-Gal A deficiency) Indicated in adults, children, and adolescents aged 8 years and older
Dosage forms	Each vial contains 3.5 mL of 1 mg/mL concentrate for solution for infusion	Each vial contains 5 mg or 35 mg powder for concentrate that is reconstituted in water for injections to a concentration of 5 mg/mL
Dosing and administration	Administered at a dose of 0.2 mg/kg body weight every other week by IV infusion ▪ Infusion should be administered over 40 minutes using an IV line with an integral filter ▪ Agalsidase alfa should not be infused in the same IV line with other agents	Recommended dose is 1 mg/kg body weight administered once every other week by IV infusion ▪ Initial infusion rate should be ≤0.25 mg/min to minimise the risk of IARs ▪ Home infusion may be considered for patients tolerating their infusions well; dose and rate should remain constant, and patients experiencing AEs in a home setting must stop the infusion and seek medical attention
Summary of Efficacy Data **(Summary of Product Characteristics)**	The safety and efficacy of Replagal was assessed in two randomised, double blind, placebo controlled studies and open label extension studies, in a total of 40 patients with Fabry Disease. After 6 months of therapy there was a significant reduction in pain in the Replagal treated patients compared with placebo (p=0.021), as measured by the Brief Pain Inventory. This was associated with a significant reduction in chronic neuropathic pain medication use and number of days on pain medication. After 6 months of therapy Replagal stabilised renal function compared with a decline in placebo treated patients. After 12 to 18 months of maintenance therapy, Replagal improved renal function as measured by inulin based glomerular filtration rate by 8.7 ± 3.7 ml/min. (p=0.030). Longer term therapy (48-54 months) resulted in stabilisation of GFR in male patients with normal baseline GFR (≥ 90 mL/min/1.73 m2) and with mild to moderate renal dysfunction (GFR 60 to < 90 mL/min/1.73 m2), and in slowing of the rate of decline in renal function and progression to end-stage renal disease in male Fabry patients with more severe renal dysfunction (GFR 30 to < 60 mL/min/1.73 m^2). In a second study, fifteen patients with left ventricular hypertrophy completed a 6 month placebo controlled study and entered an extension study. Treatment with Replagal resulted in an 11.5 g decrease in left ventricular mass as measured by magnetic resonance	Efficacy and safety of Fabrazyme was evaluated in one study with children, one dose-finding study, two double-blind placebo-controlled studies, and one open-label extension study in both male and female patients. In the first placebo-controlled clinical trial, Fabrazyme was effective in clearing GL-3 from the vascular endothelium of the kidney after 20 weeks of treatment. This clearance was achieved in 69% (20/29) of the Fabrazyme treated patients, but in none of the placebo patients (p<0.001). This finding was further supported by a statistically significant decrease in GL-3 inclusions in kidney, heart and skin combined and in the individual organs in patients treated with agalsidase beta compared to placebo patients (p<0.001). Sustained clearance of GL-3 from kidney vascular endothelium upon agalsidase beta treatment was demonstrated further in the open label extension of this trial. This was achieved in 47 of the 49 patients (96%) with available information at month 6, and in 8 of the 8 patients (100%) with available information at the end of the study (up to a total of 5 years of treatment). Clearance of GL-3 was also achieved in several other cell types from the kidney. Plasma GL-3 levels rapidly normalised with treatment and remained normal through 5 years. Renal function, as measured by glomerular filtration rate and serum

	Agalsidase alfa (Replagal)	Agalsidase beta (Fabrazyme)
	imaging (MRI) in the controlled study, while patients receiving placebo exhibited an increase in left ventricular mass of 21.8 g. In addition, in the first study involving 25 patients, Replagal effected a significant reduction in cardiac mass after 12 to 18 months of maintenance therapy ($p<0.001$). Subsequent open label studies demonstrated significant reduction from baseline in left ventricular mass by echocardiography in both male and female Fabry patients over 24 to 36 months of Replagal treatment. Compared with placebo, treatment with Replagal also reduced accumulation of GL3. After the first 6 months of therapy mean decreases of approximately 20 - 50 % were observed in plasma, urine sediment, liver, kidney, and heart biopsy samples. After 12 to 18 months treatment a reduction of 50 –80% was observed in plasma and urine sediment.	creatinine, as well as proteinuria, remained stable in the majority of the patients. However, the effect of Fabrazyme treatment on the kidney function was limited in some patients with advanced renal disease. Another double-blind, placebo-controlled study of 82 patients was performed to determine whether Fabrazyme would reduce the rate of occurrence of renal, cardiac, or cerebrovascular disease or death. The rate of clinical events was substantially lower among Fabrazyme-treated patients compared to placebo-treated patients (risk reduction = 53% intent-to-treat population ($p=0.058$); risk reduction = 61 % per-protocol population ($p=0.034$)). This result was consistent across renal, cardiac and cerebrovascular events (individually none reached statistical significance (Banikazemi et al., 2007)).
Special warnings and precautions	Idiosyncratic IARs: Among patients in clinical trials, ≥1 idiosyncratic IAR was experienced by: ▪ 13.7% of adult patients (n=177) ▪ 23.5% of paediatric patients ≥7 years of age (n=17) ▪ 37.5% of paediatric patients <7 years of age (n=8) Onset of IARs typically occurred within 2 to 4 months of the first infusion, and effects decreased over time Common symptoms of idiosyncratic IARs included pyrexia, rigors, tachycardia, urticaria, nausea/vomiting, angioneurotic oedema with throat tightness, stridor, and swollen tongue In the event of mild to moderate IARs: ▪ Immediate medical attention should be obtained ▪ The infusion may be halted until symptoms subside and restarted after 5 to 10 minutes ▪ Treatment with preventative medication may prevent subsequent IARs (see “premedication”) Serious infusion reactions were not common. In patients with preexisting cardiac manifestations of Fabry disease, IARs may trigger cardiac events. Hypersensitivity reactions: Hypersensitivity reactions to agalsidase alfa have been reported	IARs: Among patients in clinical trials, ≥1 IAR was experienced by 67% of patients ▪ Re-administration of agalsidase beta in these patients should be performed with caution ▪ Antibody status should be regularly monitored IAR frequency decreased with time. After experiencing an IAR, patients were able to continue therapy by decreasing the infusion rate (~0.15 mg/min) and taking preventative medication (see “premedication”). Hypersensitivity: Hypersensitivity reactions are possible. Immediate (Type I) hypersensitivity reactions have occurred in a small number of patients. In the event of severe allergic reactions or anaphylaxis, agalsidase beta should be discontinued immediately. Immunogenicity: As agalsidase beta is a protein product, IgG antibody development is expected (see “seroconversion”, below). Patients with advanced renal disease: Agalsidase beta may have limited effect in patients with advanced renal disease.

	Agalsidase alfa (Replagal)	Agalsidase beta (Fabrazyme)
	In the event of severe hypersensitivity or anaphylaxis, agalsidase alfa should be discontinued immediately Antibodies to the protein: As agalsidase alfa is a protein product, patients may develop antibodies (see "seroconversion", below)	
Seroconversion	~24% of male patients treated with agalsidase alfa developed a low titre IgG response ▪ Antibodies developed after ~3 to 12 months ▪ 17% of patients remained IgG positive after 12 to 54 months ▪ 7% of patients developed tolerance In paediatric patients >7 years: IgG antibodies were detected in 1/16 male patients, with no increased incidence of AEs In paediatric patients <7 years: IgG antibodies were detected in 0/7 male patients IgE positivity (borderline) has been reported in a very limited number of patients in clinical trials of agalsidase alfa, but not associated with anaphylaxis.	IgG antibodies were detected in the majority of patients treated with agalsidase beta ▪ Antibodies typically developed within 3 months of the first infusion ▪ 40% of patients experienced a ≥4-fold titre reduction ▪ 14% of patients developed tolerance ▪ 35% of patients experienced a titre plateau IgE positivity has been detected in 6 patients in clinical trials of agalsidase beta ▪ All 6 patients were eventually able to continue on agalsidase beta after a re-challenge protocol (1/2 the therapeutic dose at 1/25 the recommended rate, gradually titrated upwards as tolerated).
Common AEs (≥1/100)	IARs were the most commonly reported AEs, occurring in 13.7% of adult patients ▪ AEs were generally similar in paediatric patients, with more frequent IARs and pain exacerbation Common AEs reported in clinical trials (N=177): ▪ Cardiac: tachycardia, palpitations ▪ Vascular: flushing, hypertension ▪ Nervous system: headache, dizziness, dysgeusia, neuropathic pain, tremor, hypersomnia, hypoesthesia, paraesthesia ▪ Ear and labyrinth: tinnitus, aggravated tinnitus ▪ Eye: decreased corneal reflex, increased lacrimation ▪ General and administration site: rigors, pyrexia, pain and discomfort, fatigue, aggravated fatigue, feeling hot, feeling cold, asthenia, chest pain, chest tightness, influenza-like illness, injection site rash, malaise ▪ GI: nausea, diarrhoea, vomiting, abdominal pain/discomfort ▪ Metabolism and nutrition: peripheral oedema ▪ Musculoskeletal/connective tissue/bone: musculoskeletal discomfort, myalgia, back pain, limb pain, peripheral swelling,	IARs occurred in the majority of patients, with 67% of patients experiencing ≥1 IAR ▪ Patients who have developed IgG antibodies have a greater risk of IARs Anaphylaxis has occurred in the postmarketing setting Common AEs reported in clinical trials (N=168): ▪ Cardiac: tachycardia, palpitations, bradycardia ▪ Vascular: flushing, hypertension, pallor, hypotension, hot flush ▪ Nervous system: headache, paraesthesia, dizziness, somnolence, hypoesthesia, burning sensation, lethargy, syncope ▪ Ear and labyrinth: tinnitus, vertigo ▪ Eye: increased lacrimation ▪ General and administration site: chills, pyrexia, feeling cold, fatigue, chest discomfort, feeling hot, peripheral oedema, pain, asthenia, chest pain, facial oedema, hyperthermia ▪ GI: nausea, vomiting, abdominal pain, upper abdominal pain, abdominal discomfort, stomach discomfort, oral hypoesthesia, diarrhoea ▪ Musculoskeletal and connective tissue: pain in extremity, myalgia,

	Agalsidase alfa (Replagal)	Agalsidase beta (Fabrazyme)
	arthralgia, joint swelling ▪ Respiratory/thoracic/mediastinal: cough, hoarseness, throat tightness, dyspnoea, nasopharyngitis, pharyngitis, increase throat secretion, rhinorrhoea ▪ Skin and subcutaneous tissue: acne, erythema, pruritus, rash, livedo reticularis	back pain, muscle spasms, arthralgia, muscle tightness, musculoskeletal stiffness ▪ Respiratory/thoracic/mediastinal: dyspnoea, nasal congestion, throat tightness, wheezing, cough, exacerbated dyspnoea ▪ Skin and subcutaneous tissue: pruritus, urticarial, rash, erythema, generalised pruritus, angioneurotic oedema, swelling face, maculopapular rash
Premedication	Following an IAR requiring symptomatic treatment, pretreatment with antihistamines and/or corticosteroids, administered orally or IV between 1 and 24 hours before infusion, may be used to prevent subsequent IARs	In patients who have experienced mild or moderate IARs, pretreatment with antihistamines, paracetamol, ibuprofen, and/or corticosteroids have allowed continuation of agalsidase beta therapy
Drug interactions	Contraindicated with drugs that inhibit intracellular α-gal A activity (e.g. chloroquine, benoquin, amiodarone, gentamicin)	Contraindicated with drugs that inhibit intracellular α-gal A activity (e.g. chloroquine, benoquin, amiodarone, gentamicin)

α-gal-A=alpha-galactosidase A; AE=adverse event; GI=gastrointestinal; IAR=infusion-associated reaction; Ig=immunoglobulin; IV=intravenous.
Source: (Genzyme Therapeutics, 2014; Shire, 2006; Fox, 2012)

Table B8.2: Criteria for starting and stopping enzyme replacement therapy

UK Adult Fabry Disease Standard Operating Procedures (Hughes et al., 2013a)	
Criteria for starting ERT	**Criteria for stopping or not starting ERT**
In males with classical mutations (leucocyte enzyme activity <1%) ERT should commence at diagnosis. In females and those males with 'later onset' mutations with higher levels of leucocyte enzyme activity enzyme replacement therapy should commence when one of the following criteria are fulfilled: 1. General symptoms of Fabry disease, specifically -Uncontrolled pain leading to a need to alter lifestyle or pain that interferes with quality of life 2. Evidence of renal disease a. Clinically significant reduction in Glomerular Filtration Rate (< 80 ml/min adjusted according to age) b. In males Proteinuria >300 mgs/24 hours. c. In males Microalbuminuria where a renal biopsy showed endothelial deposits, vascular or interstitial changes d. In children: persistent microalbuminuria. 3. Evidence of cardiac disease A. ECG ▪ Presence of left ventricular hypertrophy (Romhilt-Estes or Cornell criteria); Isolated repolarisation abnormalities (in absence of other causes); Conduction abnormalities: (Short PR interval, 1, 2 or 3 degree heart block, bundle branch block) B. Echocardiogram ▪ Increased left ventricular mass (in patients with concentric remodelling or hypertrophy); increased left ventricular wall thickness (13 mm in any segment); Left atrial enlargement; Valvular thickening/insufficiency; Systolic impairment; Diastolic dysfunction C. Arrhythmia: 24 hour ECG (or other documented ECG evidence) showing bradyarrhythmia, atrial arrhythmia, ventricular tachycardia. D. Ischaemic heart disease: positive exercise test, PET scan in the ABSENCE of angiographically significant epicardial coronary artery disease. 4. Evidence of Neurovascular disease: Previous stroke or TIA in the absence of other risk factors; Progression of abnormal cerebral MRI scans 5. Gastrointestinal symptoms such as pain, vomiting or altered bowel habit which are significantly reducing quality of life and not attributable to other pathology.	**Stop:** GENERAL: 1. Intolerable and unavoidable adverse effects. 2. Intercurrent illness, where either long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for Fabry disease. 3. At the request of the patient, or properly allocated guardian acting in the patient's best interests. 4. If the circumstances of the patient's lifestyle are such that sufficient compliance with treatment is not possible. 5. If the health and wellbeing of medical and/or nursing staff are placed under significant threat as a result of the actions or lifestyle of the patient. 6. Emigration of the patient outside the jurisdiction of the UK. SPECIFIC: (considered annually from the first anniversary of start of ERT) Objective evidence of progression in measured clinical criteria which are not (1) Attributable to a secondary pathology (2) Commensurate with natural age-related decline (3) Remediable by increasing dose, changing product or institution of other simple therapeutic measure (4) Within the normal measured variation of that laboratory parameter (5) Out weighed in clinical significance by stabilisation or improvement in one of the other criteria. On the basis of current major criteria these might include: a. Worsening of pain beyond baseline b. Deterioration of GFR or proteinuria (20% decline) c. Progressive impairment of systolic or diastolic dysfunction resulting in worsening heart failure symptoms d. New presentation of clinically significant neurovascular disease **Do not start:** 1. The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy. 2. Patients with Fabry disease who are deemed too severely affected to benefit from ERT 3. ESRD requiring dialysis in the absence of other starting criteria 4.Severe cardiac fibrosis/ ICD/PM in the absence of other starting criteria

European Fabry Working Group Delphi consensus panel (Biegstraaten et al., 2015)	
Criteria for starting ERT	**Criteria for stopping or not starting ERT**

Males ≥16 years old with classic Fabry disease without signs or symptoms (class IIB)
Upon early signs of organ involvement consistent with Fabry disease and not fully explained by other pathology (males and females with classic Fabry disease and males with non-classic Fabry disease: class I; females with non-classic Fabry disease D: class IIB)
<u>Organ system-specific criteria:</u>
Renal
▪ Microalbuminuria according to KDIGO criteria (males: class I; females: class IIB)
▪ Proteinuria according to KDIGO criteria (males: class I; females: class IIB)
▪ Renal insufficiency:
  ▪ GFR 60 to 90 mL/min/1.73 m^2, corrected for age (>40 years: −1 mL/min/1.73 m^2/year) (males with classic Fabry disease: class I; males with non-classic Fabry disease and females with classic Fabry disease: class IIA; females with non-classic Fabry disease: class IIB)
  ▪ GFR 45 to 60 mL/min/1.73 m^2, corrected for age (>40 years: −1 mL/min/1.73 m^2/year) (class IIB)
Cardiac
▪ Cardiac hypertrophy (MWT >12 mm) without or only minimal signs of fibrosis (class I)
▪ Signs of cardiac rhythm disturbances (sinus bradycardia, atrial fibrillation, repolarization disorders) (class I)
CNS
▪ WMLs (class IIB)
▪ TIA/stroke (class IIA)
▪ Hearing loss, corrected for age (class IIB)
Pain
▪ Neuropathic pain (class IIA) OR neuropathic pain even if completely controlled (i.e., not interfering with daily activities) with pain medication (class IIB)
GI
▪ GI symptoms (class IIA if <16 years old; class IIB if >16 years old)
	Stop
	▪ Non-compliance >50% of infusions (class I)
	▪ Failure to attend follow-up visits regularly (per local guidelines) (class I)
	▪ Persistent life-threatening or severe IARs that do not respond to prophylaxis (e.g. anaphylaxis) (class I)
	▪ ESRD without option for renal transplantation, in combination with advanced heart failure (NYHA class IV) (class IIA)
	▪ End-stage Fabry disease or other comorbidities with life expectancy <1 year (class IIB)
	▪ Severe cognitive decline, any cause (class IIB)
	▪ Lack of response for 1 year when sole indication for ERT is neuropathic pain while receiving maximum supportive care (class IIB); does not apply to male patients with the classic phenotype
	Do not start
	▪ Advanced cardiac disease with extensive fibrosis if cardiac disease consistent with Fabry disease and not fully explained by other pathology is sole treatment indication (class I)
	▪ ESRD without option for renal transplantation, in combination with advanced heart failure (NYHA class IV) (class IIA)
	▪ End-stage Fabry disease or other comorbidities with life expectancy <1 year (class IIB)
	▪ Severe cognitive decline, any cause (class IIB)

Evidence Levels: Criteria were included if there was ≥75% agreement and no disagreement among the panel Class I: evidence and/or general agreement that the treatment or procedure is beneficial, useful, effective; is recommended/ indicated; Class II: conflicting evidence and/or diverging opinions on usefulness/effectiveness of treatment or procedure; is recommended/indicated; Class IIA: Weight of evidence/opinion is in favour of usefulness/effectiveness; should be considered; Class IIB: Usefulness/ effectiveness is not as well established by evidence/opinion; may be considered; Class III: Evidence/general agreement that treatment/ procedure is not useful/effective, and in some cases may be harmful; is not recommended; treatment should not generally be withheld for patients on dialysis or patients with cognitive decline; decisions on stopping or not starting treatment should be made carefully for each individual
ESRD: end-stage renal disease, FD: Fabry Disease, GFR: glomular filtration rate, GI: gastro-intestinal, KDIGO: Kidney Disease/Improving Global Outcomes, MWT: mean ventricular wall thickness, TIA: transient ischemic attack, WML: white mass lesion

Symptomatic therapy

As ERT does not reverse end-organ damage that has already occurred, patients must also receive a variety of therapies targeting their specific symptoms (e.g. cardiac disease, renal disease, pain, etc.). The recommended schedule of assessments, treatment goals, and therapy options by organ system are presented in Table B8.3.

Table B8.3: Recommended assessments and treatment options for management of Fabry disease symptoms

Assessment	Recommendation	Treatment and goals of therapy
Cardiac		
Palpitations/angina ▪ Holter and 30-day event monitoring ▪ Coronary angiography	Baseline; every 6 months ▪ If arrhythmia or palpitations are present ▪ If clinical signs of angina	Goals of treatment are to decrease cardiac-related morbidity or mortality, and delay need for pacemaker or defibrillator ▪ Hypertension: ACEIs, CCBs ▪ Dyslipidaemia: statins ▪ Atrial fibrillation: antiarrhythmic drugs ▪ Endothelium dysfunction with vasospasm and thrombotic events: ACEIs, CCBs, anti-platelet drugs ▪ Symptomatic bradycardia or tachycardia, or higher degree of AV block: permanent cardiac pacing ▪ LV outflow tract obstruction: verapamil (conservative management); interventional techniques (if conservative measures are ineffective) ▪ Coronary artery disease: beta blockers (monitor for worsening bradycardia); interventions ▪ Heart failure: diuretics ▪ Advanced heart failure: transplantation
Blood pressure/heart rhythm	Every visit	
ECG and 2D echocardiography with Doppler	Baseline and every other year until age 35, then every year	
Renal		
Serum electrolytes; creatinine; BUN ▪ 24-hour or spot urine for total protein/creatinine; albumin/creatinine; sodium; creatinine	Baseline and then: ▪ If CKD stage 1/2 and >1 g/d proteinuria, or CKD stage 4, every 3 months ▪ If CKD stage 3, every 6 months ▪ If CKD stage 1/2 and <1 g/d proteinuria, every 12 months	Goals of therapy are stabilisation of renal function, minimisation of urinary protein and albumin excretion, and control of blood pressure Treatment goals vary based on initial renal function (e.g., baseline GFR and proteinuria) ▪ Proteinuria: ACEIs and ARBs ▪ ESRD: dialysis or transplantation
Neurologic		
Neurologic exam; Brief Pain/McGill Pain Inventory	Baseline; every 6 months	Treatment goals include pain management (e.g. reduced need for pain medication, reduction in pain interference with activities of daily living) and minimisation of stroke and TIA risk ▪ Painful crises and paraesthesia's: phenytoin, carbamazepine, oxcarbazepine, gabapentin, pregabalin, and/or topiramate, as well as SNRIs; limit activity that precipitates pain
Paraesthesia's; fatigue; fever; sweating; heat/cold intolerance; joint pains; stroke symptoms; TIA	Baseline; every 6 months	
Brain MRI	Baseline ▪ At time of TIA or stroke	
Magnetic resonance angiography	To exclude cerebral vasculopathy	

Assessment	Recommendation	Treatment and goals of therapy
Cold/heat intolerance; pain; vibratory thresholds; sweat output; post-ganglionic sudomotor function; superficial skin blood flow	If available	▪ Painful crises (acute management): opioids ▪ Stroke prevention: platelet-inhibiting agents (e.g., aspirin, clopidogrel, ticlopidine); proper hydration and vitamin intake
Stroke risk factors ▪ Cholesterol; triglycerides ▪ Lipoprotein A; total plasma homocysteine, factor V Leiden, Protein C; Protein S, prothrombin G20210A; antithrombin III; anticardiolipin antibody; lupus anticoagulant	▪ Annually ▪ Baseline	
Dermatologic		
—	—	▪ Angiokeratoma: laser methods can be considered; more pedunculated lesions may require liquid nitrogen treatment
ENT		
Tinnitus; hearing loss; vertigo; dizziness	Baseline; every 6 months	Improved hearing (in patients with hearing loss) or maintained hearing (in patients in the normal range) are goals of therapy ▪ Sudden hearing loss: vasodilators and steroids ▪ Advanced deafness: hearing aids/cochlear implants ▪ Vertigo with nausea: anti-nausea drugs (e.g., trimethobenzamide, prochlorperazine)
Audiometry; tympanometry; otoacoustic emissions	Baseline; yearly	
GI		
Postprandial abdominal pain; bloating; diarrhoea; nausea; vomiting; early satiety; difficulty gaining weight	Baseline; every 6 months	Therapy goals include decreased occurrence and severity of diarrhoea and/or abdominal pain ▪ Delayed gastric emptying: metoclopramide; small, frequent meals ▪ Dyspepsia: H_2 blockers; diet restrictions
Endoscopic/radiographic evaluation	If symptoms persist/worsen	
Ophthalmologic		
Visual disturbance; light sensitivity	Baseline; every 6 months	Ocular manifestations of Fabry disease rarely require treatment
General exam	Baseline; every 12 months	
Retinal dysfunction testing; tear secretion testing	If indicated	
Pulmonology		
Cough; exertional dyspnoea; wheezing; exercise intolerance	Baseline; every 6 months	▪ Airway obstruction: bronchodilators ▪ Significant pulmonary symptoms: bronchoscopy/lung biopsy to rule out other causes
Spirometry; treadmill exercise testing; oximetry; chest X-ray	Baseline; every 2 years ▪ More frequently if indicated	
Skeletal		

Assessment	Recommendation	Treatment and goals of therapy
Bone mineral density	Baseline	Goal of therapy is to prevent osteoporotic fractures
General		
General status; school/work performance; sports; depression; anxiety; drug use; pedigree update; somatic growth	Baseline; every 6 months	▪ Depression/anxiety/drug use: Specialist referral, SSRI
Complete physical exam; SF-36 or PedsQL	Baseline; every 6 months	
Genetic counselling	Baseline; every 6 months for new issues	

ACEI=angiotension-converting enzyme inhibitor; ARB=angiotensin receptor blocker; AV=atrioventricular; BUN=blood urea nitrogen; CKD=chronic kidney disease; ECG=electrocardiogram; ENT=ear, nose and throat; ESRD=end-stage renal disease; GFR=glomerular filtration rate; GI=gastrointestinal; H_2=histamine type 2; LV=left ventricular; MRI=magnetic resonance imaging; PedsQL=Pediatric Quality of Life Inventory; SF-36=Short Form-36 Health Survey; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TIA=transient ischemic attack.
Source: (Eng et al., 2006; Nagueh, 2014; Mehta et al., 2010a, 2010b; Burlina et al., 2011)

Limitations of current therapy

Infusion reactions

ERT commonly causes IARs that can be unpleasant for patients and that disrupt therapy. IARs can include fever, chills, rigors, flushing, fatigue, headache, nausea, and dyspepsia (Germain, 2010). While the cause of IARs is unknown, it may have a relation to antibodies, as IARs are noted to be more frequent in antibody-positive patients (Germain, 2010; Genzyme Therapeutics, 2014; Wilcox et al., 2012). The product labelling notes that IARs occurred in 13.7% of patients receiving agalsidase alfa and 67% of patients receiving agalsidase beta (Genzyme Therapeutics, 2014; Shire, 2006).

The incidence of IARs is greatest during the early months of treatment, but IARs can be unpredictable and have occurred in later infusions in patients who did not experience IARs with previous infusions (Genzyme Therapeutics, 2014; Shire, 2006; Germain, 2010). In some cases, the severity of the IAR means that the infusion must be discontinued (Genzyme Therapeutics, 2014; Shire, 2006). A study conducted by Amicus indicated that a person would be willing to forgo 1.18 years of life to choose a treatment for Fabry disease that was not associated with infusion reactions 12 times per year (for further detail see Section 10.1.9).

Burden of IV infusions

The short half-life of manufactured α-Gal A means that frequent (biweekly) infusions are necessary (Genzyme Therapeutics, 2014; Shire, 2006). These lifelong biweekly infusions can represent a substantial burden to patients and their families.

- When performed at an infusion centre, requiring patients and their families to travel, this can interfere with work, school, or family obligations. For example, infusion centre schedules may have limited flexibility, time is often lost waiting, and overall an infusion that takes only 2 hours may end up consuming an entire day (Parini et al., 2010).

- While home infusions are more convenient for many patients, medical support is often required (Ramaswami, 2011; Cousins et al., 2008). Furthermore, only patients who have had successful initial infusions in an infusion centre and also fulfil certain requirements (patient is clinically stable and not subject to IARs, appropriate medical support is available, etc.) are candidates for home infusion (Cousins et al., 2008). Some patients are also uncomfortable with the greater responsibility placed on them or family members with home infusions, or have concerns about safety (Parini et al., 2010; Milligan et al., 2006).
- [redacted]
- In a discrete choice experiement (DCE) to evaluate preferences for treatment of Fabry disease, participants expressed a strong preference for an oral treatment over an infusion treatment such that they would be willing to forgo 1.8-1.9 years of life for an every-other-day tablet (see Section 10.1.9).
- IV infusions are also associated with a low but significant risk of infections (Borgwardt et al., 2013).

Neutralising antibodies

Since ERT is a recombinant protein, patients may develop antibodies to the protein (Genzyme Therapeutics, 2014; Shire, 2006). A variety of data show that neutralising antibodies develop in response to infusions of agalsidase alfa and agalsidase beta. IgG antibodies have been detected in the majority of patients treated with agalsidase beta, whilst ~24% of male patients treated with agalsidase alfa developed a low titre IgG response (Table B8.1). Generally, studies show that antibodies develop more commonly in men than in women. In a recent study, the frequency of serum-mediated galsidase inhibition (i.e. development of endogenous neutralising antibodies) was 40% in agalsidase-treated males, independent of the compound initially used (agalsidase-alfa or –beta) (Lenders et al., 2015).

Several studies have shown that the presence of neutralising antibodies affects GL3 and lyso-Gb3 levels and increases the risk for IARs (Rombach et al., 2012; Vedder et al., 2008; Wilcox et al., 2012; Linthorst et al., 2004). Furthermore, agalsidase inhibition has been shown to be associated with worse disease severity scores (Lenders et al., 2015). Compared with agalsidase inhibition-negative men, agalsidase inhibition-positive men showed greater left ventricular mass (p=0.02) and substantially lower renal function (difference in eGFR of about –30 ml/min per 1.73m^2; p=0.04), which was confirmed by a longitudinal 5-year retrospective analysis. Additionally, affected patients presented more often with Fabry disease-typical symptoms, such as diarrhoea, fatigue, and neuropathic pain and tinnitus (Lenders et al., 2015). These results suggest that in patients who have developed neutralising antibodies, the efficacy of ERT is impaired, which would not be the case with migalastat therapy.

In the DCE, participants expressed a statistically significant preference for avoidance of risk of antibody formation but to a lesser extent that preferences for avoidance of infusions and

reactions (see Section 10.1.9). This is likely due to not fully appreciating the clinical implications of antibody formation and the subsquest impact on disease progression.

Long-term ERT and disease progression

ERT has been demonstrated to reduce disease substrate with beneficial effects on symptoms and progression as well as long-term outcomes. A prospective study of 57 patients treated with either agalsidase alfa or beta for approximately 5 years suggests that the risk of a first or second renal, cardiac, or cerebrovascular event decreased with increasing treatment duration (Rombach et al., 2013b). A recent cohort study that included 289 adult Fabry patients in England found that time on ERT was significantly associated with a decrease in LVMi; a reduction in the risk of proteinuria and, in those without baseline proteinuria, a small increase in eGFR (Anderson et al., 2014). Long term data on the efficacy of ERT from patient registries has also been recently reported. Data from the Fabry Outcome Survey, showed that in 740 patients treated with agalsidase alfa over a median of approximately 5 years, that the decline in renal function and progression of left ventricular hypertrophy was slowed in treated patients. Morbidity occurred later in treated patients, with an approximately 16% risk of a composite morbidity event (26% in males) after 24 months with ERT versus approximately 45% without treatment. In addition the estimated median survival in treated males was 77.5 years versus 60 years in untreated males (Beck et al., 2015).

Although the evidence show that ERT is effective in the long term, accumulation of disease substrate can still continue, gradually resulting in symptom progression and tissue damage, and clinically meaningful events continue to occur in patients receiving ERT (Patel et al., 2011; Weidemann et al., 2013a; Askari et al., 2007; Warnock et al., 2012). As mentioned above the presence of neutralising antibodies has been shown to affect GL3 and lyso-Gb3 levels and has been shown to be associated with worse disease severity scores (Rombach et al., 2012; Vedder et al., 2008; Wilcox et al., 2012; Linthorst et al., 2004; Lenders et al., 2015).

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Diagnostic delays

As noted previously, the common initial signs and symptoms of classic Fabry disease typically manifest in childhood (pain, fever, inability to sweat, fatigue, and exercise intolerance), but a diagnosis often is not made until the disease has progressed for years or decades, at which point organ damage has already occurred. For example, approximately 20% of cases of Fabry disease are diagnosed by nephrologists when patients are in their late 20s, after the disease process has been underway for years (Mahmud, 2014). Clinical experts in the UK estimated that approximately 50% of patients remain undiagnosed (Amicus Therapeutics, 2016a).

Diagnosis of Fabry disease can be difficult due to the wide range of symptoms experienced by individual patients (Germain, 2010). Because the clinical manifestations of Fabry disease often resemble those of other, more common diseases, careful differential diagnosis is important in order to allow prompt initiation of appropriate treatment. However, as noted

previously, angiokeratoma and whorl-shaped lesions in the cornea, although seemingly minor symptoms, are hallmarks of Fabry disease, and physician awareness of their significance can aid in diagnosis (Sivley, 2013; Germain, 2010).

Overall, mean diagnostic delays have been shown to range from 12 to 20 years for both males and females (Mehta et al., 2004; Schiffmann et al., 2009; Martins et al., 2013). These delays represent the loss of a meaningful opportunity to reduce the impact of this serious and progressive condition through appropriate treatment. Illustrating this, is the fact that higher baseline proteinuria levels, which were associated with older age, have been associated with more rapid kidney disease progression (Schiffmann et al., 2009). Earlier diagnosis and prompt initiation of appropriate treatment could slow disease progression and thus the requirements for healthcare resources targeting the serious complications of Fabry disease, as well as improve quality of life (El-Abassi et al., 2014; Schiffmann et al., 2009).

A known family history of Fabry disease may prompt more rapid recognition of signs and symptoms, and earlier diagnosis (Ellaway, 2014).

Current therapy

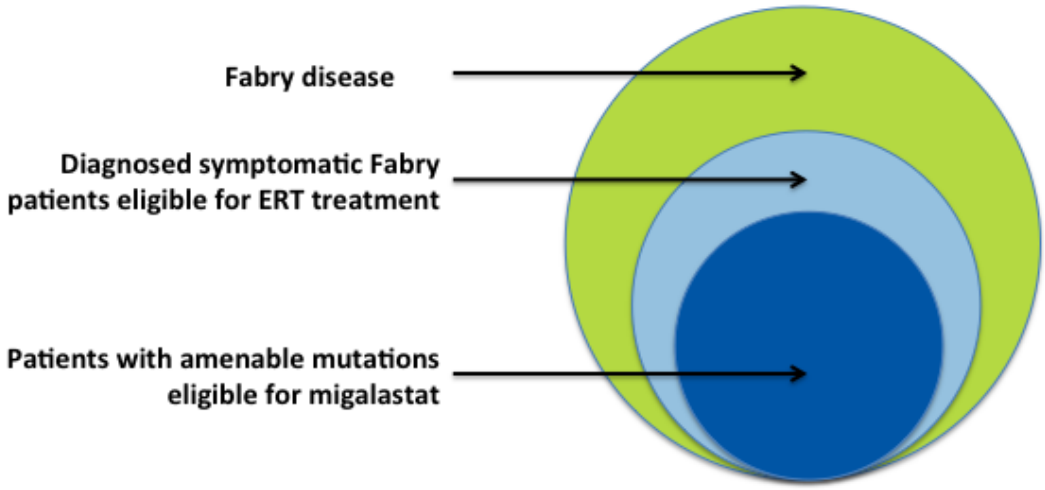
During interviews with clinical experts, several points were raised concerning current treatment (Amicus Therapeutics, 2016a):

- Despite the availability of guidelines there is some uncertainty around when is it appropriate to stop treatment with ERT, since the criteria are less well defined than starting criteria.
- Testing for neutralising antibodies is not carried out routinely and there are no protocols for tolerisation.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

The pathway of care is expected to remain unchanged, and migalastat would simply offer an alternative oral treatment option for Fabry patients with an amenable mutation who might otherwise receive intravenous ERT therapy. It is estimated that approximately 30% to 50% of patients with Fabry disease have mutations that are amenable for migalastat therapy (Figure B8.2)(Benjamin et al., 2009; Filoni et al., 2010; Germain et al., 2012; Shabbeer et al., 2006; Ishii et al., 2007; Wu et al., 2011).

Figure B8.2: Patient population eligible for migalastat



During the clinical program, *GLA* mutations were analysed for their responsiveness to migalastat, a process that is continuing (this process is described in Section 9.4.1). To date (October 2015), 268 mutant forms of α-Gal A have been determined to be amenable to migalastat therapy (Benjamin et al., 2016).

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Migalastat is a first-in-class, oral, innovative chaperone that provides personalised genetically targeted therapy for Fabry patients with amenable mutations.

In LSDs such as Fabry disease, a mutation in a patient's own (endogenous) enzyme may lead to a decrease in protein stability, and even misfolding or unfolding of the enzyme. This instability and unfolding of endogenous enzyme causes it to lose activity and may disrupt proper trafficking of the enzyme to lysosomes where it is needed to degrade the lipid substrate.

Pharmacological chaperones as monotherapy agents are designed to bind to the endogenous target enzyme, stabilising the enzyme in its properly folded active form and facilitating cellular trafficking to lysosomes before unbinding from the enzyme. It essentially rescues the body's own enzyme. This allows for increased activity, improved cellular function and potentially reduced cell stress.

With its unique mechanism of action, migalastat addresses unmet needs that remain for patients with amenable mutations. Migalastat:

- Avoids the burden of chronic lifelong ERT infusion therapy for the patient and the patients' families
- Avoids the risks of ERT infusion-associated reactions and infections, and removes the need for pre-infusion medications

- Avoids the immune response associated with ERT
- Has broader tissue distribution than ERT
- Chaperones endogenous α-Gal A, which more closely mimics natural enzyme trafficking than the every-other-week infusions of manufactured ERT

As an orally administered therapy, migalastat increases patient choice, reduces pressure on homecare and infusion services and offers greater patient convenience.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

No change in the way current service are organised or delivered is foreseen, however the introduction of migalastat is expected to remove some of the pressure from infusion clinics and lessen the need for delivery of infusions by homecare nurses. As described above in Section 8.4 migalastat would increase the range of treatment options for those patients with Fabry disease who have amenable mutations.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional genetic testing is required by the NHS to identify patients eligible for migalastat, or for ongoing monitoring of patients (Amicus Therapeutics, 2016a).

In order to facilitate identification of patients eligible for therapy with migalastat, Amicus has developed a pharmacogenetic reference table (the Migalastat Amenability Table) that lists all known amenable and non-amenable mutations.

- As part of the standard diagnostic process for Fabry disease, patients undergo genetic testing to confirm the presence of a *GLA* mutation.
- Physicians can then compare the patient's genetic testing results with the Migalastat Amenability Table, which is published and updated on an ongoing basis by Amicus Therapeutics. The Migalastat Amenability Table, and a table of non-amenable mutations, can be found in the draft Summary of Product Characteristics. Not all mutations have been tested to date. If a patient's mutation does not appear in either the table of amenable mutations or table of non-amenable mutations, physicians will be advised to contact Amicus for further information. Amicus will provide an amenability test at no cost.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure are required.

Standard genetic testing for Fabry disease can identify the mutation, and Amicus Therapeutics has developed a database of mutations amenable to migalastat, a process that is on-going. Although the number of mutations that will be amenable to migalastat will increase over time, the overall total number of patients receiving treatment either with migalastat or ERT will not increase, except for new incident cases of Fabry being diagnosed, since migalastat is only intended to be used in patients eligible for treatment in the existing guidelines. The testing of new samples for mutations that are amenable to migalastat would be performed regularly by Amicus at the company's expense and the list of amenable mutations updated.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

It is not foreseen that any tests or investigation would no longer be needed. The use of migalastat in patients who would otherwise receive ERT would mean patients having fewer invasive intravenous infusions and therefore the number of homecare nurses required to administer, and re-train venous access technique for ERT infusions in Fabry patients would be reduced.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

The following section describes a single systematic search of the literature that was conducted to identify studies of interest reporting **clinical efficacy and safety, HRQL, and economic evidence**. Prisma diagrams have been generated to show the number of publications identified in each category (i.e. one for clinical efficacy and safety, one for HRQL and one for economic studies). Searches were conducted in the following databases to identify literature published from database inception to December 2015:

- MEDLINE (via PubMed)
- Embase
- The Cochrane National Health Service Economic Evaluation Database (NHS EED)
- The Cochrane Health Technology Assessment (HTA) Database
- The Database of Abstracts of Reviews of Effects (DARE)[1]
- EconLit

[1] National Institute for Health Research (NIHR) funding to produce DARE and NHS EED ceased at the end of March 2015; however, both databases can still be accessed via the Centre for Reviews and Dissemination (CRD) website. Searches of MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsychInfo and PubMed were continued until the end of 2014. Bibliographic records were published on DARE and NHS EED until 31st March 2015. The HTA database will continue to be produced by CRD for the foreseeable future.

There was no publication date limit applied for the published literature database searches. Information from clinical trials registers and conference proceedings was limited to 2013 to 2015. Publications identified from the manual checking of reference lists of relevant systematic literature reviews was limited to 2015.

Supplementary searches of “grey” literature were performed to complement the literature database searches and provide data from recent or ongoing trials. Sources for these searches included:

- Registers of clinical trials: clinicaltrials.gov, clinicaltrialsregister.eu, the United States (US) Food and Drug Administration (FDA) website, European Medicines Agency (EMA) website, National Institute for Health and Care Excellence (NICE) website, UKMPS Society website, and websites of manufacturers of comparator products for migalastat

- A search of conference proceedings: American Society of Nephrology (ASN), American Society of Human Genetics (ASHG), Annual Clinical Genetics Meeting (ACGM), European Society of Human Genetics (ESHG), Fabry Nephropathy Update, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting, ISPOR Annual European Congress, Lysosomal Disease Network (LDN), Society for the Study of Inborn Errors of Metabolism (SSIEM).

Manual checking of the references lists of relevant systematic literature reviews was also carried out.

For specific details of the search strategies, please see section 17.1.4.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Sources of unpublished data relevant to the NICE scope (draft manuscripts and clinical study reports) were provided by the sponsor, and were assessed according to the same criteria as described for the published sources (please see Section 9.1.1 and Section 17).

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

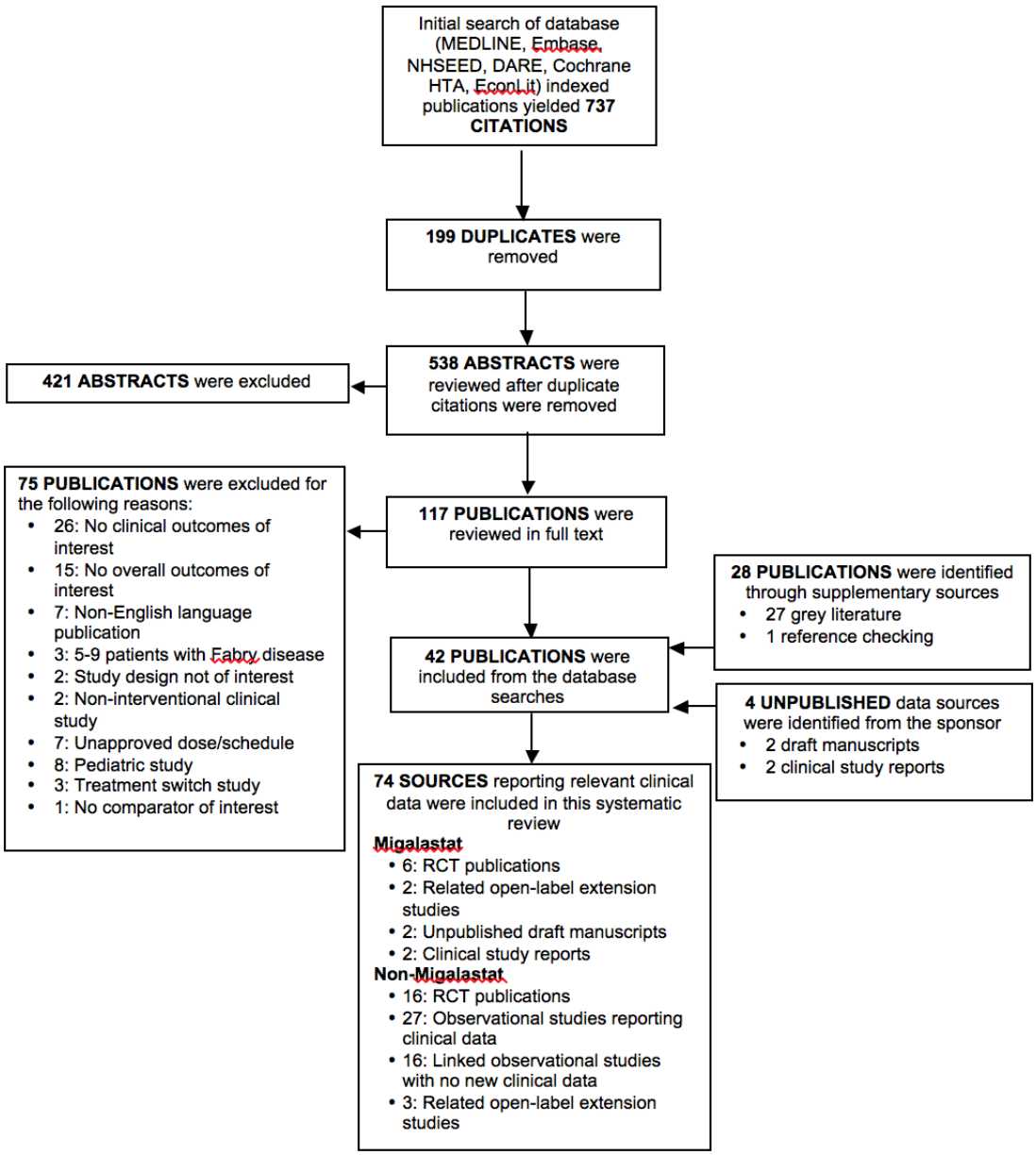
Table C9.1: Selection criteria used for published studies

	Population	Interventions and Comparators	Outcomes	Study Design
Inclusion criteria	• At least 10 adults with Fabry disease	• Any/all pharmacological therapies aimed at primary treatment of Fabry disease	**Clinical** • Efficacy, such as: ○ Renal function ○ Cardiac events ○ Cerebrovascular events ○ GL-3 levels • Safety and tolerability, such as: ○ Overall, severe, or serious AEs ○ Discontinuations (all cause, due to AEs, due to lack of efficacy) ○ Mortality **Quality of life,** such as: • SF-36 • EQ-5D • Pain	• Prospective interventional trials (including RCTs) • Observational studies (including patient registries) • Retrospective analyses
Exclusion criteria	• Patients with conditions other than Fabry disease	• Non-interventional • Non-pharmacological treatment • Treatment of sequelae of Fabry disease • Non-approved doses or schedules of treatment for Fabry disease	• No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes • Outcomes not reported for Fabry patients only in studies with a mixed population	• Narrative literature reviews, expert opinions, letters to the editor, editorials, or consensus reports • Case reports or case series of fewer than 10 patients • *In vitro*, animal, genetic, or foetal studies • Studies reporting only pooled data for patients from multiple study designs (RCTs, registries, open-

				label extensions) • Studies reporting treatment switching between types of ERT

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure C9.1: PRISMA Study Attrition Diagram for Clinical Studies



Please note: The 12 sources reporting migalasat data are shown in Table C9.6.

Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C9.2: Selection criteria used for unpublished studies

	Population	Interventions and Comparators	Outcomes	Study Design
Inclusion criteria	• At least 10 adults with Fabry disease	• Any/all pharmacological therapies aimed at primary treatment of Fabry disease	**Clinical** • Efficacy, such as: ○ Renal function ○ Cardiac events ○ Cerebrovascular events ○ GL-3 levels • Safety and tolerability, such as: ○ Overall, severe, or serious AEs ○ Discontinuations (all cause, due to AEs, due to lack of efficacy) ○ Mortality **Quality of life,** such as: • SF-36 • EQ-5D • Pain	• Prospective interventional trials (including RCTs) • Observational studies (including patient registries) • Retrospective analyses
Exclusion criteria	• Patients with conditions other than Fabry disease	• Non-interventional • Non-pharmacological treatment • Treatment of sequelae of Fabry disease • Non-approved doses or schedules of treatment for Fabry disease	• No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes • Outcomes not reported for Fabry patients only in studies with a mixed population	• Narrative literature reviews, expert opinions, letters to the editor, editorials, or consensus reports • Case reports or case series of fewer than 10 patients • *In vitro*, animal, genetic, or foetal studies • Studies reporting only pooled data for patients from multiple study designs (RCTs, registries, open-label extensions)

				• Studies reporting treatment switching between types of ERT

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Please see section 9.2.2.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Overview of the clinical development program

The clinical development program for migalastat comprises 20 trials involving 386 subjects (Amicus Therapeutics, 2015c). Of these trials, 10 were phase 1 studies involving 218 healthy subjects and 24 subjects with renal impairment. Of the 168 patients receiving migalastat in phase 2 and phase 3 trials, 119 have been treated for >1 year and one patient has been treated for 9 years (Schiffmann et al., 2015b; Amicus Therapeutics, 2015b). For use as monotherapy, the development program includes the phase 3 trials summarised in Table C9.3 (Amicus Therapeutics, 2015c).

The systematic review of the literature identified two unpublished studies for migalastat for which data was available (ATTRACT and FACETS). Following completion of the SLR, data became available from the open-label study AT1001-041. For completeness, AT1001-41 and its successor, AT1001-042 have been included in the table below. Detailed methodology is not presented for these studies. No data is yet available from AT1001-042.

Table C9.3: List of relevant published and unpublished studies for migalastat

Primary study reference/ Data source	Study name	Population	Description	Primary endpoint/ planned assessments	Treatment groups (Intervention/ Comparator)
Phase 3					
ATTRACT Study Investigators (Draft Manuscript)	AT1001-012 ATTRACT (NCT01218659)	Fabry patients, 16-74 years old, who had received ERT for at least 12 months (ITT n=60)	18-month active comparator, open-label study vs. ERT followed by a 12-month OLE in which all patients received migalastat	Annualised change in GFR from baseline to 18 months	During the 18-month active-comparator study, ERT-experienced patients (≥12 months prior continuous ERT use) either: • Switched from ERT to migalastat HCl 150 mg QOD • Remained on ERT
Germain et al (Submitted Manuscript)(Germain et al., Draft Manuscript)	AT1001-011 FACETS (NCT00925301)	67	6-month placebo-controlled double-blind period followed by a 6-month OLE during which all patients migalastat and an optional 12-month OLE	Proportion of patients with a ≥50% reduction from baseline to 6 months in kidney IC GL3 inclusions	Patients who were either ERT-naïve or had no ERT for ≥6 months were randomised to: • Migalastat HCl 150 mg QOD • Placebo
Amicus Therapeutics, Data on File (Summary of Clinical Efficacy, 2015)	AT1001-041 (NCT01458119)	[redacted] patients originally enrolled are continuing in AT1001-042)	OLE study for patients in ATTRACT, FACETS, and FAB-CL-205 Study was terminated for administrative reasons	Change from baseline in $eGFR_{CKD-EPI}$ and cardiac parameters	Migalastat HCl 150 mg QOD
No data available	AT1001-042 (NCT02194985)	[redacted] ([redacted] from FACETS/041, [redacted] from ATTRACT/041 and 10 from FAB-CL-201)	OLE successor to AT1001-041 Study is ongoing	Change from baseline in $eGFR_{CKD-EPI}$ and cardiac parameters	Migalastat HCl 150 mg QOD

* Numbers as of 5th February 2016

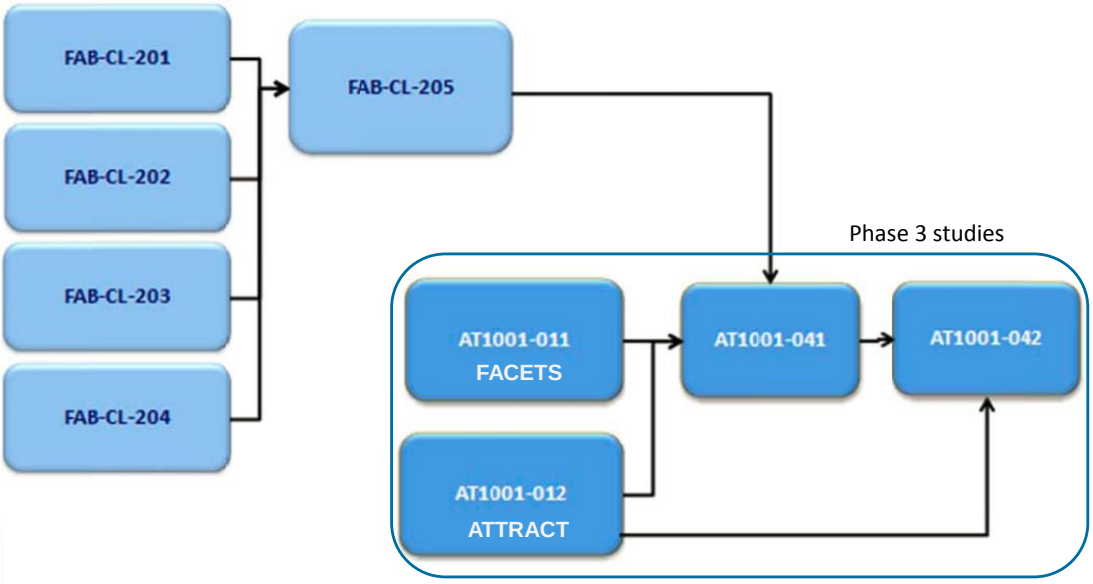
9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

None of the relevant published studies have been excluded.

The phase 2 monotherapy trials were designed to evaluate the safety, tolerability, and pharmacodynamics (PD) of migalastat in patients with Fabry disease and to help determine the appropriate dose for the phase 3 trials. Studies FAB-CL-202 and FAB-CL-203 have been reported as combined results by Germain et al (Germain et al., 2012) and study FAB-CL-204 has been reported by Giugliani et al (Giugliani et al., 2013). Study FAB-CL-201 did not evaluate the proposed migalastat HCl 150 mg once every other day (QOD) dose, and these data have not been published. These studies are not described in further detail in this section since they are single arm or dose-ranging studies and do not provide comparison with an active comparator or placebo.

Figure C9.2 shows the phase 2 and phase 3 trials and how they relate to each other. Studies FAB-CL-205 and AT1001-042 are currently ongoing.

Figure C9.2: Migalastat monotherapy clinical program



9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

ATTRACT (Study 012) Study Methodology

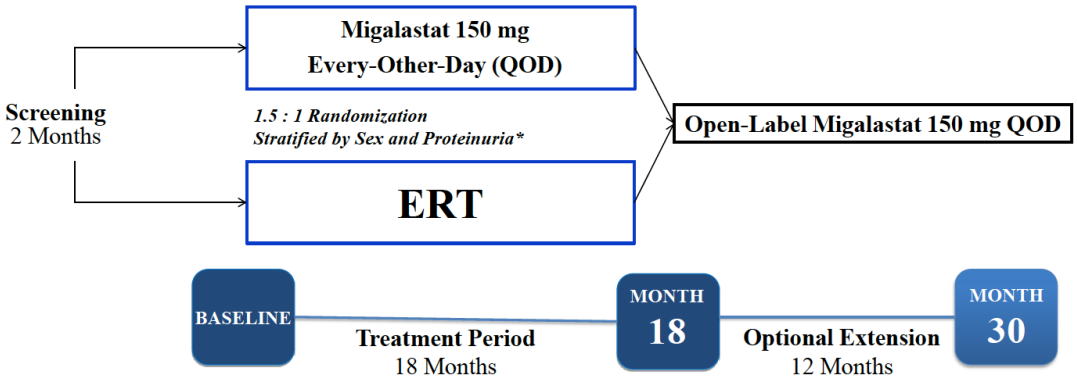
The pivotal trial AT1001-012, ATTRACT (**AT**1001 **T**herapy Compared to Enzyme **R**eplacement in Fabry Patients with **A**T1001-responsive Mutations: a Global **C**linical **T**rial), was conducted to evaluate the efficacy of migalastat compared to ERT for the treatment of Fabry disease in patients who have an amenable mutation and were previously treated with ERT (Amicus Therapeutics, 2015c; ATTRACT Draft Manuscript).

ATTRACT is an active-controlled, randomised, open-label, multinational study that was designed in collaboration with the European Medicines Agency (EMA). Patients in the trial had Fabry disease and were receiving either agalsidase alfa or agalsidase beta. Following a 2-month screening period, 60 patients were stratified by gender and degree of proteinuria (low: <0.1 g/24 hours; high: ≥0.1 g/24 hours) and randomised into 2 groups in a 1.5:1 ratio (ATTRACT Draft Manuscript):

- 36 patients were switched from ERT to migalastat HCl 150 mg QOD
- 24 patients continued on ERT

Patients received treatment for 18 months, after which they were eligible for a 12-month open-label extension (OLE) in which all patients received migalastat.

Figure C9.3: ATTRACT Study Design



*Proteinuria stratification: high (≥0.1 g/24h) low (≤0.1 g/24h)

The co-primary efficacy outcome measures assessed renal function, which is impaired in most patients with Fabry disease. Because there is a greater risk of renal function decline in patients with higher levels of urinary protein excretion, the patients were stratified by level of proteinuria. The co-primary endpoints were the annualised change in GFR (mL/min/1.73 m^2/year) from baseline to 18 months assessed by 2 methods (Table C9.4).

A standard non-inferiority analysis comparing migalastat and ERT on the co-primary endpoints was not possible due to the small sample size. Therefore, pre-specified criteria were developed 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 (ATTRACT Draft Manuscript):

- 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%

Table C9.4: Summary of methodology for the ATTRACT randomised controlled trial

Study name	ATTRACT (AT1001-012)
Objectives	To compare the safety and efficacy of migalastat to ERT in male and female patients with Fabry disease and amenable mutations who have been previously treated with ERT
Location	This study was conducted at 25 study centres in 10 countries: Australia, Austria, Belgium, Brazil, Denmark, France, Italy, Japan, the UK, and the US.
Design	Randomised, open-label, active-controlled study
Duration of study	Each subject's study participation lasted up to approximately 21 months, including a screening/baseline period (approximately 2 months), an open-label treatment period (approximately 18 months), and a follow-up period (1 month).
Sample size	60
Inclusion criteria	• 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
Exclusion criteria	• Kidney or any solid organ transplant, or scheduled for such transplant • Regular dialysis specifically for treatment of CKD • TIA, stroke, UA, or MI within 3 months before visit 1 • Clinically significant unstable cardiac disease (e.g., symptomatic arrhythmia, UA, NYHA class III or IV CHF) • 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 with 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
Method of randomisation	Following written informed consent and eligibility and baseline assessments, patients were stratified by proteinuria (high≥0.1 g/24-hours or low<0.1 g/24-hours) and gender, and randomised into the 18-month controlled period. Patients previously treated with ERT for at least 12 months were randomised by interactive

	voice response system in a 1.5:1 ratio to switch to migalastat HCl (150 mg, every other day) or continue with ERT.
Method of blinding	This study was open-label, so blinding procedures were not performed.
Intervention(s) (n =) and comparator(s) (n =)	Migalastat (n = 36) ERT (n = 24)
Baseline differences	At baseline, the treatment groups were balanced with respect to age, race, prior use of ACEIs and ARBs, years since diagnosis of Fabry disease, GFR, and 24-hour urine protein.
Duration of follow-up, lost to follow-up information	After the open-label treatment period (approximately 18 months), patients completed a follow-up period of 1 month. No patients were lost to follow-up during the study period.
Statistical tests	The annualised rate of changes in $mGFR_{iohexol}$ and $eGFR_{CKD-EPI}$ from baseline to month 18 was analysed using an ANCOVA model with the following factors and covariates: treatment group, sex, age, baseline GFR ($mGFR_{iohexol}$ or $eGFR_{CKD-EPI}$) and baseline 24-hour urine protein. Descriptive statistics on the annualised rate of change from baseline to month 18 were generated for each treatment group from this ANCOVA model, including least squares means and 95% CIs.
Primary outcomes (including scoring methods and timings of assessments)	The co-primary endpoints were the annualised change in GFR (mL/min/1.73 m^2/year) from baseline to 18 months assessed by 2 methods. • Measurement of iohexol clearance ($mGFR_{iohexol}$): In this technique, patients received an intravenous (IV) dose of iohexol, an x-ray contrast medium that is excreted exclusively through the kidney. Blood samples were taken at several points from 2 to 4 hours following administration of iohexol, and its plasma concentration was measured. • Estimation using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula ($eGFR_{CKD-EPI}$): In this technique, serum creatinine (SCr) was measured and eGFR calculated. This method is less invasive than the iohexol clearance method and thus can be performed more frequently, lessening the potential for variability. It is the more commonly used method.
Secondary outcomes (including scoring methods and timings of assessments)	• **Annualised change in eGFR** from baseline to month 18($eGFR_{MDRD}$): eGFR was calculated using values from a standardised serum creatinine assay. • Change from baseline to month 18 in $mGFR_{iohexol}$ /$eGFR_{CKD-EPI}$/ $eGFR_{MDRD}$ • Change from baseline to month 18 in 24-hour urine protein and 24-hour urine albumin:creatinine ratio • **Composite clinical outcome**, as assessed by the number of subjects who experienced any of the following events: o Renal events: ▪ A decrease in $eGFR_{CKD-EPI}$ ≥ 15 mL/min/1.73 m^2, with the decreased eGFR < 90 mL/min/1.73 m^2 relative to Baseline ▪ An increase in 24-hour urine protein ≥ 33%, with the increased protein ≥ 300 mg relative to Baseline o Cardiac events: ▪ Myocardial infarction

        - Unstable cardiac angina, as defined by the American College of Cardiology/American Heart Association (ACC/AHA) national practice guidelines
        - New symptomatic arrhythmia requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation
        - Congestive heart failure, New York Heart Association (NYHA) class III or IV
      - Cerebrovascular events:
        - Stroke
        - Transient ischemic attack
      - Death
- **ECHO parameters** were assessed through blinded, centralised evaluation (Cardiocore, Rockville, MD). Changes from baseline to month 18 were calculated for LV mass index, LVEF, (both secondary) LV mass, LV posterior wall thickness diastolic, intraventricular septum thickness diastolic, and fractional shortening. Peak mitral inflow velocity (E and A) and the mitral valve E/A ratio were calculated by pulsed wave Doppler.
- **White blood cell (WBC) α-Gal A activity**, change from baseline
- **PROs**: Changes from baseline in 2 questionnaires (Short Form Health Survey with 36 questions, version 2 (SF-36 v2) and the Brief Pain Inventory (BPI) short form – Pain Severity Component) were summarised using descriptive statistics.
- **Plasma lyso-Gb3:** Plasma was assayed for lyso-Gb3 by liquid chromatography-mass-spectroscopy using the same plasma samples collected for the mGFRiohexol assessment at baseline and months 6, 12, and 18.

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CHF=congestive heart failure; CKD=chronic kidney disease; ERT=enzyme replacement therapy; (e)GFR = (estimated) glomerular filtration rate; $eGFR_{CKD\text{-}EPI}$ = Chronic Kidney Disease Epidemiology Collaboration; $eGFR_{MDRD}$ = Estimated glomerular filtration rate based on MDRD equation; HCl = hydrochloride; HEK = human embryonic kidney-293; MDRD = Modification of Diet in Renal Disease; $mGFR_{iohexol}$ = Iohexol clearance; NR = Not reported; PRO = Patient-reported outcome; GFR=glomerular filtration rate; *GLA*=gene for alpha galactosidase A; MI=myocardial infarction; NYHA=New York Heart Association; TIA=transient ischemic attack; UA=unstable angina.
Source: (Amicus Therapeutics, 2015d; ATTRACT Draft Manuscript)

FACETS (STUDY 011) Study Methodology

Pivotal trial AT1001-011, FACETS (**F**abry **A**T1001 **C**haperone **E**fficacy, **T**herapeutics, and **S**afety Study), was conducted to evaluate the efficacy, safety, and PD of migalastat in patients with amenable mutations who were ERT-naïve (had either never received ERT or had not received ERT for at least 6 months prior to screening).

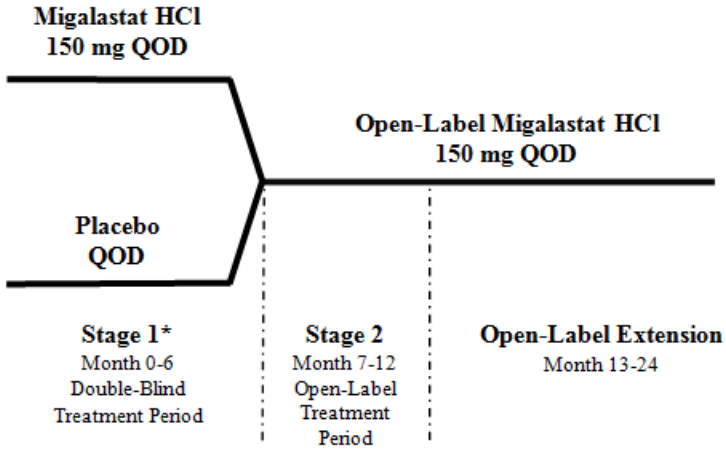
FACETS was a double-blind, placebo-controlled, 6-month study followed by a 6-month OLE and a 12-month OLE. For the 6-month double-blind trial (Stage 1), 67 patients were randomised to (Germain et al., Draft Manuscript):

- migalastat HCl 150 mg QOD (n=34)
- placebo QOD (n=33)

After the 6-month, double-blind, placebo-controlled Stage 1, patients continued in a 6-month OLE in which all patients received migalastat (Stage 2). This was followed by a 12-month

OLE. During the OLE, neither the patients nor the investigators knew what treatment patients had received during the double-blind Stage 1.

Figure C9.4: FACETS Study Design



* 1:1 Randomization; stratified by gender

HCl = hydrochloride; QOD = every other day

The primary outcome measure was the percentage of patients in each treatment group who responded to treatment, defined as a ≥50% reduction in kidney interstitial capillary (IC) GL3 inclusions (Germain et al., Draft Manuscript).

Table C9.5: Summary of methodology for the FACETS randomised controlled trial

Study name	FACETS (AT1001-011)
Objectives	To evaluate the safety and efficacy of migalastat in male and female patients with Fabry disease
Location	International study, included US, Australia, France, Italy
Design	Randomised, double-blind, placebo-controlled study
Duration of study	6 months
Sample size	67
Inclusion criteria	• 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 (ULN) 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
Exclusion criteria	• Undergone or was scheduled to undergo kidney transplantation, or was currently on dialysis • eGFR < 30 mL/min/1.73m2 (chronic kidney disease [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 intercurrent 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
Method of randomisation	Following informed consent and eligibility/baseline assessments, patients were randomised 1:1 into 6-month, double-blind 150 mg migalastat HCl or placebo every other day. No other details were reported.
Method of blinding	NR; assessors were blinded to treatment/visit.
Intervention(s) (n =) and comparator(s) (n =)	Migalastat (n = 34) Placebo (n = 33)
Baseline differences	Groups were balanced, with 24-hour protein (mg±SEM) being 452±109 in the placebo and 342±79 in migalastat group. Major differences noted within groups were: **ACEI/ARB/RI use: n (%)** Migalastat: 6 (18) Placebo: 13 (39) **Prior ERT (≥6 months before baseline): n (%)** Migalastat: 5 (15) Placebo: 12 (36)
Duration of follow-up, lost to follow-up information	The FACETS study included 2 stages: stage 1 was the RCT for 6 months and was followed by stage 2 open-label migalastat for 18 months. Patients were followed through the second stage of the trial, with the exception of 1 patient randomised to migalastat who withdrew consent after completing stage 1.
Statistical tests	Statistical analysis plan population included all randomised patients using the responsiveness criteria of the preliminary HEK assay. The Cochran Mantel Haenszel test was used for the primary endpoint and an ANCOVA model with covariate adjustment for baseline value and factors for treatment group and treatment by baseline interaction was used for the other endpoints. The ANCOVA model was also used for the *post hoc* analyses comparing the baseline to month 6 changes in mean number of GL-3 inclusions per interstitial capillary as a continuous variable.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the kidney histology assessments: Proportion in each treatment group achieving a ≥50% reduction in GL-3 inclusions/interstitial capillary from baseline to month 6. It was quantitatively assessed in 300 capillaries by 3 independent expert pathologists blinded to treatment/visit. Other GL-3 changes (podocyte, endothelial and mesangial cells) and glomerular sclerosis were assessed qualitatively.

Secondary outcomes (including scoring methods and timings of assessments)	Stage 1 secondary outcomes: • **Urine GL3**: 24-hour urine GL3 was analysed by liquid chromatography-mass spectroscopy • **Renal function**: Annualised rates of change (mL/min/1.73m²/year) were calculated using the $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and $mGFR_{iohexol}$ methods. • 24-hour urine protein, albumin, and creatinine • IC GL3 inclusions (percent change) Other Stage 1 endpoints were: • Median change from baseline to month 6 in GL-3 inclusions/interstitial capillary and change in percentage of interstitial capillaries with zero GL-3 inclusions. • Plasma lyso-Gb3 analysed by liquid chromatography-mass spectroscopy. • Echocardiography: Parameters were assessed through blinded, centralised evaluation. • PRO: Changes from baseline to month 6 in PROs were assessed using the Gastrointestinal-Symptoms-Rating-Scale, Short Form-36v2^{TM} and BPI-Pain-Severity-Component. The key efficacy endpoints specified in the Stage 2 SAP for Stage 2 of the study were as follows: • IC GL-3 inclusions durability of response in Stage 2 as measured by the mean change for subjects with amenable mutations who received migalastat in Stage 1 (migalastat-migalastat group) • Mean change in IC GL3 inclusions in Stage 2 for subjects with amenable mutations who received placebo in Stage 1 (placebo-migalastat group) • Renal function (eGFR) annualised rate of change • Changes in other exploratory kidney histology assessments (podocyte, mesangial cell, and endothelial cell GL3)

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CHF=congestive heart failure; CKD=chronic kidney disease; ERT=enzyme replacement therapy; GFR=glomerular filtration rate; *GLA*=gene for alpha galactosidase A; MI=myocardial infarction; NYHA=New York Heart Association; TIA=transient ischemic attack; UA=unstable angina.
Source: (Amicus Therapeutics, 2015a)

Identification of amenable mutations

The in vitro assay that is used to identify responsive (amenable) mutations involves human embryonic kidney (HEK) cells and has evolved over the duration of the clinical trial program.

Clinical trial HEK assay

The first assay (called the clinical trial HEK assay) was developed during the phase 2 trials. In this assay, the genetic sequence of mutated α-Gal A was transfected into HEK cells, which then produced mutated α-Gal A. The cells were incubated with and without migalastat. The enzymatic activity and levels of α-Gal A were evaluated with a fluorescent technique and with western blot analysis (Wu et al., 2011; Benjamin et al., 2011). An increase in α-Gal A and its activity indicates that the mutant enzyme was stabilised by migalastat and trafficked to the lysosome.

This assay was used to enrol patients for the phase 3 trials. In order to develop criteria for categorising a mutation as amenable for the phase 3 trials, the results from phase 2 trials for the clinical trial HEK assay were compared with the results from incubating the peripheral blood mononuclear cells (PBMC) of phase 2 participants with migalastat (Barlow et al., 2014). These data were used in conjunction with information from the literature that has shown that an increase of only 1% to 5% of normal (wild-type) activity in vivo is necessary to produce a clinically meaningful result (Desnick, 2004). Based on these concepts, the criteria used to categorise a mutation as amenable for the phase 3 trial enrolment were a relative increase in α-Gal A activity ≥1.2 fold above baseline with an absolute increase of ≥3% after incubation with 10 mcM migalastat.84 The 10 mcM concentration was chosen for the assay because it is the approximate maximum plasma concentration of migalastat achieved following a single oral dose of 150 mg (Johnson et al., 2013).

Migalastat Amenability Assay

While the phase 3 studies were ongoing, the clinical trial HEK assay was transferred to a third party for Good Laboratory Practice (GLP) validation and to satisfy regulatory guidance. Minor modifications were made in terms of how the assay is conducted and its precision, but the criteria for determining an amenable mutation (relative increase in α-Gal A activity ≥1.2 fold above baseline with an absolute increase of ≥3% after incubation with 10 mcM migalastat) are the same (Amicus Therapeutics, 2015b; Barlow et al., 2014). This validated assay is termed the ***Migalastat Amenability Assay***.

The assay was clinically validated by comparing data from the analysis of the 268 identified mutations from pharmacodynamic results from phase 2 and 3 clinical trials, which encompassed 73 mutations. These comparisons showed that mutant α-Gal A responses in vitro had high sensitivity (how often an amenable mutation is identified as amenable) and specificity (how often a non-amenable mutation is identified as non-amenable), as well as high positive and negative predictivity (the probability that the result is correct). The Migalastat Amenability Assay results were also predictive of decreases in kidney GL3 in male patients and of plasma lyso-Gb3 values in both male and female patients. Furthermore, the changes seen in the assay for the 268 mutations were not significantly different from the responses seen in the 51 amenable mutations in the patients in the phase 2 and 3 trials.

These results establish that the Migalastat Amenability Assay is a clinically valid method of identifying mutations that will be responsive to migalastat therapy (Benjamin et al., 2016). Physicians can compare the results of the standard genetic tests their patients undergo with the data in the Migalastat Amenability Table, which was developed based on the results of the Migalastat Amenability Assay, to determine if the mutation will be responsive to migalastat, with no additional patient samples required.

Dosing

Each capsule contains migalastat HCl equivalent to 123 mg of migalastat, the active ingredient; 123 mg migalastat is equivalent to 150 mg of migalastat HCl, the formulation and dose used in the clinical trial program (Amicus Therapeutics, 2016c, 2015b). Throughout Section 9, “migalastat HCl” is used when referring to a specific dose.

Efficacy outcome measures

The efficacy endpoints in the Phase 3 studies were focused on assessing renal function, cardiac parameters, composite clinical outcomes, and patient-reported outcomes:

Measures of renal function

- Progressive decline in renal function is a major complication of Fabry disease
- GFR is generally recognised as the standard for measuring renal function in the general population (Stevens et al., 2006)
    - In Fabry disease, analysis of GFR is supported by a large amount of natural history data, with the progressive decline in GFR (and kidney function) well understood (Waldek and Feriozzi, 2014)
    - In patients with Fabry disease, the progressive decrease in GFR has also been shown to be a major risk for cardiac events (Talbot et al., 2015)
    - Estimated GFR (eGFR) based on serum creatinine concentration has been established as a reliable measure to monitor the progression of chronic kidney disease in clinical trials (Stevens and Levey, 2009)
    - Estimated GFR is also commonly used to routinely monitor renal function in clinical practice and in clinical trials in Fabry disease
    - Measured GFR (mGFR) using urinary or plasma clearance of exogenous filtration markers has been considered as the gold standard for determining renal function in an individual patient at a given time, however it is associated with some limitations. The invasiveness of the technique means that it is not feasible to determine mGFR frequently, thereby contributing to variability in the results. In addition, mGFR is affected by external factors such as by exercise and diurnal variation (Stevens and Levey, 2009)
- Proteinuria is also well established as a marker of kidney function, both in the general population and in patients with Fabry disease (Schiffmann et al., 2009; Warnock et al., 2012)

Measures of cardiovascular function

- Cardiac complications are the main cause of death in Fabry disease (Waldek and Feriozzi, 2014)
    - LVH (an increase in the mass of the left ventricle) is the most common cardiac manifestation of Fabry disease, and it is an important risk factor for cardiac events (Patel et al., 2011; Kampmann et al., 2008)
- Reductions in LV mass, as shown by evaluation of LVMi, have been shown to reduce risk for cardiovascular events in patients in the general population (Maisel, 2009; Drazner, 2011; Bluemke et al., 2008; Mathew et al., 2001; Okin et al., 2004)
    - Reductions in LV mass have been shown to improve outcomes in Fabry disease (Rombach et al., 2014; Anderson et al., 2014; Weidemann et al., 2009).

Echocardiography (ECHO, with tissue Doppler imaging where available) was performed to measure LVMi, LV mass, intraventricular septum thickness diastolic (IVSTd), LV fractional shortening, LV ejection fraction, and LV posterior wall thickness (LVPWT) (Amicus Therapeutics, 2015c).

Clinical event rates

- Few trials have measured rates of renal, cardiac, or cerebrovascular events

In ATTRACT, a composite clinical outcome was assessed, based on the number of patients in each treatment group who experienced specific renal, cardiac, or cerebrovascular events, or death

Disease substrate levels

- GL3 and lyso-Gb3, two of the damaging substrates that accumulate in Fabry disease, are directly linked to the underlying genetic defect that is responsible for Fabry disease
    - Urinary GL3 decreases soon after ERT is initiated, and levels subsequently rise in patients who develop α-Gal A antibodies (Vedder et al., 2008; Schiffmann et al., 2006)
    - Plasma lyso-Gb3 has become increasingly recognised as an important marker of disease severity (Rombach et al., 2010, 2012). Levels of lyso-Gb3 been shown to correlate well with disease severity in both male and female patients and to decrease with ERT. Reductions in plasma lyso-Gb3 have been demonstrated to be associated with improved outcomes in Fabry disease (van Breemen et al., 2011). High levels of plasma lyso-Gb3 are associated with increased risk for cerebrovascular disease in males and with LVH in females with Fabry disease (Rombach et al., 2010).

In the Phase 3 migalastat clinical development programme, the number of GL3 inclusions per kidney interstitial capillary (IC) was quantitatively assessed using the Barisoni Lipid Inclusion Scoring System (BLISS), which is based on using standardised digital images of specimen slides (Amicus Therapeutics, 2015c)

In addition to measurement by histological analysis in the kidney GL3 was measured in the urine of patients using LC-MS/MS (liquid chromatography with tandem mass spectrometry) (Amicus Therapeutics, 2015c).

Plasma lyso-Gb3 was also analysed by LC-MS/MS.

α-Gal A Activity

The mechanism of action of migalastat is to bind and stabilise specific mutant forms of the enzyme α-Gal A and increase their activity in the cells of patients with Fabry disease. Activity of α-Gal A was measured in PBMCs. In some studies, PBMCs were referred to by the less specific terms of white blood cells (WBCs) or leukocytes. Measurement of α-Gal A is only carried out in males due to the heterogeneous expression in different cells in females (through random inactivation of the X chromosome, see section 6).

Patient reported outcomes

- Key patient reported outcomes include:
    - Assessment of pain, using the Brief Pain Inventory (BPI)
    - GI dysfunction, such as with the Gastrointestinal Symptoms Rating Scale GSRS
    - HRQL, such as with the SF-36

Open-label, long-term extension studies

Studies AT1001-041 and AT1001-042 are multicentre, open-label extension studies designed to provide continued migalastat treatment to patients who completed the pivotal phase 3 trials (ATTRACT and FACETS) or the FAB-CL-205 phase 2 trial:

- Both AT1001-041 and AT1001-042 are ongoing and have the same design. Study AT1001-041 was the initial open-label extension study to assess the safety and efficacy of 150 mg migalastat HCl QOD in patients who completed studies AT1001-012 (ATTRACT), AT1001-011 (FACETS), or FAB-CL-205. Study AT1001-042 is replacing AT1001-041 for logistic reasons. Eligible patients from ATTRACT, FACETS, or FAB-CL-205 could elect to continue initially into AT1001-041 and later into AT1001-042. In addition, some patients from AT1001-012 could enrol directly into AT1001-042.
- As of 5th February 2016, [redacted]

The primary objective of these extension studies is to evaluate the long-term safety of migalastat. Secondary objectives were to assess the long-term efficacy and PD of migalastat, including $eGFR_{CKD-EPI}$, cardiac parameters (including LVMi), α-Gal A activity, and patient-reported assessments (SF-36v2 and BPI – pain severity component).

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

The migalastat clinical data sources identified in the systematic literature review are shown in Table C9.6.

Table C9.6: Migalastat clinical study reference sources

Primary Study ID and Study Type (RCT versus non-RCT)	Primary Study Citation	Linked Publications	Notes for Linked Publications
FACETS (AT1001-011) RCT	Germain, D, Hughes, D., Nicholls, K., et al. Efficacy and Safety of Migalastat, an Oral Pharmacological Chaperone for Fabry Disease (submission). N Engl J Med. (Germain et al., Draft Manuscript)	**Clinical Study Report:** Amicus Therapeutics. Clinical Study Report: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacodynamics of AT1001 in Patients With Fabry Disease and AT1001-Responsive GLA Mutations (Amicus Therapeutics, 2015a)	**FACETS RCT (CSR)**
	[Unpublished manuscript submitted to *New England*	Subjects treated with migalastat continue to demonstrate stable renal function and reduced left	**FACETS RCT and OLE**

	Journal of Medicine]	ventricular mass index over 3 years in a long-term extension study of Fabry disease (Germain et al., 2015b)	
		Phase 3 and long-term extension study with migalastat, a pharmacological chaperone, demonstrate stable renal function, reduced left ventricular mass and gastrointestinal symptom improvement in patients with Fabry disease (Germain et al., 2015a)	**FACETS RCT and OLE**. From the RCT, only one gastrointestinal symptom is reported: diarrheal improvement.
		Germain D, Bichet, DG., Giugliani, R., et al. Subjects treated with migalastat demonstrate stable renal function, reduced left ventricular mass and gastrointestinal symptom improvement in Phase 3 and a long-term extension study of Fabry Disease (Germain et al., 2015c)	**FACETS RCT and OLE**. From the RCT, only one gastrointestinal symptom is reported: diarrheal improvement.
		Migalastat Reduces Plasma Globotriaosylsphingosine (lyso-Gb3) in Fabry Patients: Results from Phase 3 Clinical Studies. (Benjamin et al., 2015)	**FACETS RCT and OLE.** From the RCT, only one outcome is reported: reduction of plasma lyso-Gb3
		Subjects treated with migalastat continue to demonstrate stable renal function in a Phase 3 extension study of Fabry Disease (Bichet et al., 2014)	**FACETS RCT and OLE**
		Improvement in gastrointestinal symptoms observed in the phase 3 FACETS (AT1001-011) study of migalastat in patients affected with Fabry disease (Schiffmann et al., 2015a)	**FACETS RCT**
ATTRACT (AT1001-012) RCT	Amicus Therapeutics. Oral Pharmacological Chaperone Migalastat compared to Enzyme Replacement Therapy for Fabry Disease: 18-Month Results from the Phase 3 ATTRACT Study (ATTRACT Draft Manuscript). [Unpublished manuscript for submission]	**Clinical Study Report:** A Randomized, Open-Label Study to Compare the Efficacy and Safety of AT1001 and Enzyme Replacement Therapy (ERT) in Patients With Fabry Disease and AT1001-Responsive GLA Mutations, Who Were Previously treated With ERT (Amicus Therapeutics, 2015d)	**ATTRACT RCT (CSR)**
		Hughes D, Bichet, DG., Giugliani, R., et al. Long-term efficacy and safety of migalastat compared to enzyme replacement therapy in Fabry disease: Phase 3 study results. (Hughes et al., 2015)	**ATTRACT RCT**

		Migalastat and Enzyme Replacement Therapy Have Comparable Effects on Renal Function in Fabry Disease: Phase 3 Study Results (Nicholls et al., 2014)	**ATTRACT RCT**

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

Patient populations

The ATTRACT and FACETS studies both enrolled patients diagnosed with Fabry disease between 16 and 74 years old with Fabry disease diagnosis and confirmed *GLA* mutation responsive to migalastat in vitro. The main difference in the study populations was that in ATTRACT patients had been receiving ERT for at least 12 months whilst patients in FACETS were ERT naïve. The two study populations had comparable demographic data, including mean age, gender distribution, and race. Disease characteristics, in terms of renal and cardiac parameters, were similar between the two Phase 3 studies at baseline, with the exception of 24-h urine protein, which was numerically higher in FACETS.

Baseline Characteristics

Baseline characteristics of the ATTRACT safety population are presented in Table C9.7. The migalastat and ERT groups were comparable on baseline characteristics, including age, gender, and years since diagnosis (ATTRACT Draft Manuscript).

Baseline characteristics are shown in Table C9.8 for the FACETS ITT population. These characteristics were balanced between the 2 groups.

In both studies, the majority of both male and female patients had multi-organ disease, as shown in Table C9.9.

Table C9.7: Baseline characteristics of the ATTRACT safety population

	Migalastat (n=36)	**ERT (n=21)**	**All (N=57)**
Age (years), mean±SE	50.2±2.3	46.3±3.3	48.9±1.9
Gender			
Male, n (%)	16 (44%)	9 (43%)	25 (44%)
Female, n (%)	20 (56%)	12 (57%)	32 (56%)
Amenable *GLA* mutation, n (%)	34 (94%)	19 (90%)	53 (93%)
Years since diagnosis, mean±SE	10.2±2	13.4±2.6	11.4±1.6
24-hour protein (mg/24 hour), mean±SE	267±69	360±150	301±70
Percent with ≥100 mg urinary protein/24 hour, %	58	57	58
$mGFR_{iohexol}$ (mL/min/1.73 m^2), mean±SE	82.4±3	83.6±5.2	82.8±2.6
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2), mean±SE	89.6±3.7	95.8±4.1	91.9±2.8
$eGFR_{MDRD}$ (mL/min/1.73 m^2), mean±SE	[redacted]	[redacted]	[redacted]

	Migalastat (n=36)	ERT (n=21)	All (N=57)
ERT			
Agalsidase alfa, n (%)	[redacted]	[redacted]	[redacted]
Agalsidase beta, n (%)	[redacted]	[redacted]	[redacted]
Use of ACEI/ARB/RI, n (%)	16 (44%)	11 (52%)	27 (47%)
Patients with amenable *GLA* mutations, n (%)	34 (94%)	19 (90%)	53 (93%)

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; eGFRCKD-EPI=glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; ERT=enzyme replacement therapy; eGFRMDRD=glomerular filtration rate estimated by the Modification of Diet in Renal Disease equation; GLA=gene for alpha galactosidase A; mGFRiohexol=glomerular filtration rate measurement by iohexol clearance; RI=renin inhibitor; SE=standard error.
Source: (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015c)

Table C9.8: Baseline characteristics of the FACETS ITT Population

Parameter	Placebo (n=33)	Migalastat (n=34)	All (N=67)
Female, n (%)	21 (64)	22 (65)	43 (64)
Male, n (%)	12 (36)	12 (35)	24 (36)
Age, mean (range)	45 (24,64)	40 (16, 68)	42 (16, 68)
Years since diagnosis, mean±SE	7.1±1.4	5.7±1.2	6.3±0.89
$eGFR_{MDRD}$ (mL/min/1.73 m^2), mean±SE	88±6.5	90±4.0	89±3.8
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2), mean±SE	94±3.7	95±4.9	95±3.0
$mGFR_{iohexol}$ (mL/min/1.73 m^2), mean±SE	86±4.3	83±5.3	85±3.4
24-hour protein, mg/24 hr, mean±SE	452±109	342±79	NR
ACEI/ARB/RI use, n (%)	13 (39)	6 (18)	19 (28)
Prior treatment with ERT, n (%)	12 (36)	5 (15)	17 (25)
Patients with amenable *GLA* mutation, n (%)	22 (67)	28 (82)	50 (75)

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; $eGFR_{CKD-EPI}$=estimated glomerular filtration rate - Chronic Kidney Disease Epidemiology Collaboration; $eGFR_{MDRD}$=estimated glomerular filtration rate – Modification of Diet in Renal Disease; ERT=enzyme replacement therapy; *GLA*=gene for alpha galactosidase A; $mGFR_{iohexol}$=modified glomerular filtration rate – iohexol clearance; NR=not reported; RI=renin inhibitor; SE=standard error.
Source: (Germain et al., Draft Manuscript)

Table C9.9: Baseline assessment of disease severity

	ATTRACT (mITT population)		FACETS (amenable mutations)	
Parameter, n (%)	**Males (n=23)**	**Females (n=29)**	**Males (n=17)**	**Females (n=33)**
Fabry disease in ≥2 organ systems	[redacted]	[redacted]	[redacted]	[redacted]
Angiokeratoma[a]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac[b]	[redacted]	[redacted]	[redacted]	[redacted]
CNS[c]	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathic pain[a]	[redacted]	[redacted]	[redacted]	[redacted]
Renal[d]	[redacted]	[redacted]	[redacted]	[redacted]
GI[a]	[redacted]	[redacted]	[redacted]	[redacted]
Plasma lyso-Gb3[e]			[redacted]	[redacted]
WBC α-Gal A activity (vs. normal[h])				

	ATTRACT (mITT population)		FACETS (amenable mutations)	
Parameter, n (%)	**Males (n=23)**	**Females (n=29)**	**Males (n=17)**	**Females (n=33)**
<1%			[redacted]	[redacted]
<3%			[redacted]	

α-Gal A=alpha-galactosidase A; CNS=central nervous system; eGFR=estimated glomerular filtration rate; GI=gastrointestinal; lyso-Gb3=globotriaosylsphingosine; LVH=left ventricular hypertrophy; TIA=transient ischemic attack ; WBC=white blood cell.
[a] Based on medical history. [b] Previous cardiac event (based on medical history), LVH or conduction abnormality (based on medical history or baseline assessment). [c] Stroke, TIA, tinnitus/hearing loss in medical history.
[d] Baseline eGFR <60 mL/min/1.73 m^2, 24-hour protein >300 g, or renal impairment in medical history.
[e] Thresholds based on plasma lyso-Gb3 in a cohort of male and female Fabry patients with the classic phenotype. For male patients, the lower end of the range of plasma lyso-Gb3 was used. For female patients, plasma lyso-Gb3 values greater than the upper limit of normal were used.
[f] n=11 [g] n=20 [h] Normal WBC α-Gal A activity: 22 nmol/h/mg.
Source: (ATTRACT Draft Manuscript; Germain et al., Draft Manuscript)

The study patients with amenable mutations were classified based on the clinical phenotype associated with their *GLA* mutation (Table C9.10). Overall, the frequency of patients with mutations associated with classic and non-classic phenotypes were approximately equal in ATTRACT while patients with the classic mutation type were the most frequent in FACETS. The proportions of patients with mutations associated with each phenotype were roughly comparable for the migalastat and ERT groups in ATTRACT and the migalastat and placebo groups in FACETS (ATTRACT Draft Manuscript; Germain et al., Draft Manuscript). In ATTRACT, patients with unclassified mutations were somewhat more frequent in the ERT group compared to the migalastat group [redacted] patients had a mutation associated with both phenotypes.

Table C9.10: Fabry disease phenotypes associated with the mutations of patients in ATTRACT and FACETS (patients with amenable mutations)

	ATTRACT			FACETS		
Genotype-associated phenotype	**Migalastat (n=34)**	**ERT (n=19)**	**All (N=53)[a]**	**Placebo (n=22)**	**Migalastat (n=28)**	**All (N=50), n (%)**
Classic	[redacted]	[redacted]	[redacted]	12	18	30 (60%)
Non-classic	[redacted]	[redacted]	[redacted]	0	1	1 (2%)
Both	[redacted]	[redacted]	[redacted]	2	1	3 (6%)
Unclassified	[redacted]	[redacted]	[redacted]	8	8	16 (32%)

ERT=enzyme replacement therapy.
a N represents the population with amenable mutations. Percentages may not equal 100% due to rounding.
Source: (ATTRACT Draft Manuscript; Germain et al., Draft Manuscript)

Currently, 268 *GLA* mutations have been identified by the Migalastat Amenability Assay as amenable to migalastat therapy. [redacted] of these mutations were observed in patients randomised and treated in ATTRACT, [redacted] were observed in patients randomised in FACETS.

The patient population in the international phase 3 studies exhibited the full spectrum of severity of clinical manifestations associated with Fabry disease and are reflective of the expected treatment population in the UK.

Study methodology

ATTRACT was an active comparator study with co-primary efficacy endpoints based on renal function at 18 months, whereas FACETS was a placebo controlled study with a primary efficacy endpoint based on substrate reduction (kidney interstitial capillary GL3) at 6 months.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

The analysis sets for ATTRACT and FACETS are described in Section 9.5.

In the ATTRACT study, the primary efficacy analysis is in the modified ITT population, which included all randomised subjects with mutations amenable to migalastat in the Migalastat Amenability Assay that received at least 1 dose of study drug and had both the baseline and a post-baseline efficacy measure of mGFRiohexol and a post-baseline measure of $eGFR_{CKD-EPI}$. Randomisation in ATTRACT was stratified by sex and proteinuria (< 100 mg/24 h; ≥ 100 mg/24 h) and subgroup analyses were carried out according to these criteria (Amicus Therapeutics, 2015d).

In the FACETS study, the primary efficacy analysis is in the ITT population. Randomisation was stratified by sex. Post-hoc analysis was carried out for patients in the ITT population that had amenable mutations based on the Migalastat Amenability Assay. [redacted]

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

ATTRACT (Study 012) Patient disposition

The ATTRACT patient disposition is shown in Figure C9.5. Of the [redacted] randomised patients, [redacted] patients (each randomised to remain on ERT therapy) withdrew informed consent prior to receiving study medication and were excluded from all analyses. Therefore, the 57 randomised patients who received at least 1 dose of study medication were included in the safety population. Of these 57 patients, 53 were subsequently identified as having an amenable mutation by the Migalastat Amenability Assay (34 in the migalastat group and 19 in the ERT continuation group); the [redacted] patients in this group who also had data for $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ were categorised as the efficacy population (modified intent to treat [mITT] population) (ATTRACT Draft Manuscript). Table C9.11 summarises this information.

Of the safety population, [redacted] of patients receiving migalastat and [redacted] of patients receiving ERT completed all 18 months of the trial. The median duration of study drug was [redacted] days for migalastat and [redacted] days for ERT; compliance with study drug was [redacted] for migalastat and [redacted] for ERT (Amicus Therapeutics, 2015c).

Figure C9.5: CONSORT flow diagram ATTRACT

Table C9.11: Analysis populations in ATTRACT

Population	Migalastat	ERT	All
ITT: all randomised patients	[redacted]	[redacted]	60
Safety population: all randomised patients who received ≥1 dose of study drug	36	21	57
Patients with amenable mutations	34	19	53
mITT (efficacy population): randomised patients with amenable mutations who received ≥1 dose of study drug and had both baseline and post-baseline $mGFR_{iohexol}$ assessment and post-baseline $eGFR_{CKD-EPI}$	[redacted]	[redacted]	[redacted]
PP: all mITT patients who completed the 18-month treatment period and who did not have a change in the use of ACEIs, ARBs, or RIs	[redacted]	[redacted]	[redacted]

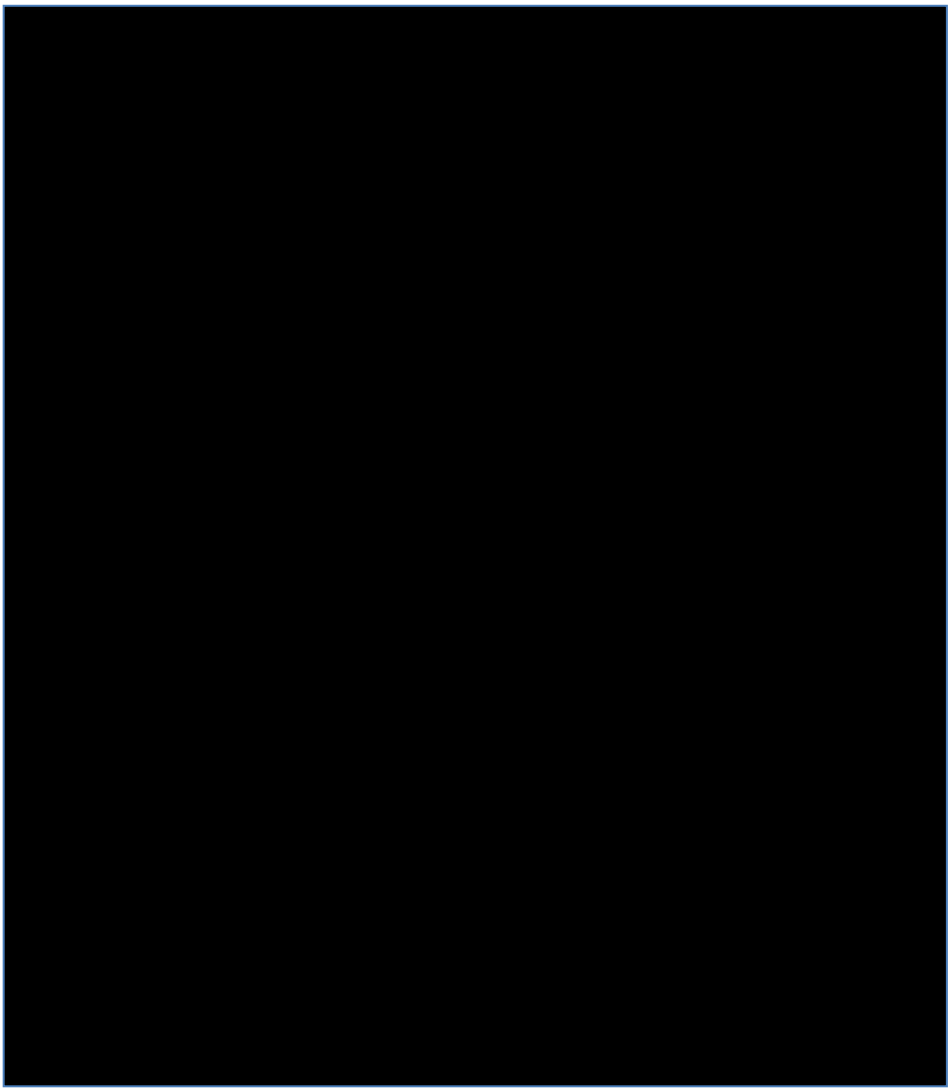
ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; eGFRCKD-EPI=glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; ERT=enzyme replacement therapy; ITT=intent to treat; mGFRiohexol=glomerular filtration rate measurement by iohexol clearance; mITT=modified intent to treat; PP=per protocol; RI=renin inhibitor.
Source: (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015d)

FACETS (Study 011) Patient disposition

The FACETS patient disposition is shown in Figure C9.6. The 67 randomised patients comprised the ITT population, which was used for the main efficacy analyses. Of these, 50

(75%) were subsequently found to have amenable mutations with the Migalastat Amenability Assay: 28 (82%) patients in the migalastat group and 22 (67%) patients in the placebo group (Germain et al., Draft Manuscript). Results are presented for both the ITT population and the population with amenable mutations.

Figure C9.6: CONSORT flow diagram FACETS



Open-label, long-term extension studies

As of 5th February 2016, [redacted] patients were receiving migalastat in AT1001-041 and [redacted] patients were enrolled in AT1001-042: [redacted]. AT1001-041 has been discontinued for administrative reasons. All patients in that study are eligible to participate in AT1001-042, and patients are directly enrolling in AT1001-042 from ATTRACT (Amicus Therapeutics, 2015c).

The baseline visit for AT1001-041 occurred at the final visit of the previous study (ATTRACT or FACETS) and clinic visits occurred every 6 months thereafter for the duration of the study. All patients received migalastat 150 mg QOD. The longest overall patient exposure to migalastat was 8.8 years (Amicus Therapeutics, 2015c).

No data are yet available for AT1001-042.

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Very few patients withdrew from the Phase 3 clinical studies. Of the 60 randomised patients in ATTRACT, 6 patients randomised to remain on ERT therapy withdrew informed consent (logistical reasons) and 2 patients randomised to migalastat (withdrew consent; depression). Of the 67 randomised patients in FACETS, 3 patients in the placebo group withdrew: 2 withdrew consent and 1 became pregnant).

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

Table C9.12: Critical appraisal of randomised control trials

Study name	**ATTRACT (AT1001-012)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	After study eligibility was confirmed at Visit 2, subjects were randomised by interactive voice response system in a 1.5:1 ratio to either stop ERT treatment and start treatment with migalastat or to continue on ERT.
Was the concealment of treatment allocation adequate?	N/A	This study was open-label, so blinding procedures were not performed.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	At baseline, the treatment groups were balanced with respect to age, race, prior use of ACEIs and ARBs, years since diagnosis of Fabry disease, GFR, and 24-hour urine protein.
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)?	No	This study was open-label, so blinding procedures were not performed.
Were there any unexpected imbalances in drop-outs between groups?	Yes	[redacted] patients randomised to remain on ERT withdrew informed consent before study medication was administered versus [redacted] who withdrew/discontinued in the migalstat arm. There was no adjustment

If so, were they explained or adjusted for?		needed for this issue.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	An ITT analysis has been carried out for the primary outcome however this is not considered to be the most appropriate analysis due to changes in the protocol for identifying amenable mutations. All outcomes have been assessed in the modified intent-to-treat population (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). [redacted]
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**FACETS (AT1001-011)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Following informed consent and eligibility/baseline assessments, patients were randomised 1:1 to either migalastat or placebo, with stratification by sex [redacted]
Was the concealment of treatment allocation adequate?	Yes	During the Stage 1 double-blind treatment period, all study drugs were identical in appearance and size. Neither the investigator nor subject knew which treatment had been assigned. The blind was maintained by placing unique identifiers on clinical supply containers to be assigned using the central randomisation system. During the double-blind treatment period (Stage 1), subjects, investigators,

		and the sponsor were blinded to treatment assignments. The blind was not to be broken during the course of the study unless, in the opinion of the investigator, it was absolutely necessary to safely treat or continue to treat the subject. Every effort was to be made to contact the sponsor before breaking the blind. The reason for breaking the blind was to be noted in the subject's medical records. Documentation of contact with the sponsor or attempted contact was also to be documented in the subject's medical records. During Stage 2, the migalastat capsules were identical in appearance and size to the Stage 1 study drugs. During Stage 2, subjects and investigators remained blinded to individual subjects' treatment assignments from Stage 1. Subjects and investigators remained blinded to treatment assignments from Stage 1 until all biopsy samples had been scored and the Stage 2 database has been locked.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Groups were balanced, with 24-hour protein (mg±SEM) being 452±109 in the placebo and 342±79 in migalastat group. Major differences noted within groups were: **ACEi/ARB/RI use: n (%)** Migalastat: 6 (18); Placebo: 13 (39) **Prior ERT (≥6 months before baseline): n (%)** Migalastat: 5 (15); Placebo: 12 (36)
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)?	Yes	Investigators, patients and assessors were blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	[redacted] There was no adjustment needed for this issue.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The statistical analysis plan population included all randomised patients using the responsiveness criteria of the preliminary HEK assay; since no drop-outs occurred, data were available for all patients.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

ATTRACT Efficacy Results

As noted previously, the efficacy analyses (mITT population) included randomised patients with amenable mutations who received ≥1 dose of study drug and had both baseline and post-baseline $mGFR_{iohexol}$ assessment and post-baseline $eGFR_{CKD\text{-}EPI}$ assessment (34 who had switched from ERT to migalastat and 18 who had continued on ERT).

Analyses of the primary efficacy parameters are also presented for the ITT population.

Summary

Table C9.13: ATTRACT Summary of primary and secondary endpoint results

Study Name		**ATTRACT**
Size of study groups (ITT)	Treatment	36
	Control	24
Study duration	Time unit: Months	18
Type of analysis	Intention-to-treat/per protocol	ITT and mITT analysis, indicated for each outcome as appropriate
Primary outcome	**Name**	**Effects on renal function – $eGFR_{CKD\text{-}EPI}$** (Annualised change in GFR from baseline to month 18) mITT population
	Unit	mL/min/1.73 m²
Effect size	Value: LS Mean ± SEM	Migalastat = -0.40±0.93 ERT = -1.03±1.29
	95% CI	Migalastat = -2.27–1.48 ERT = -3.64–1.58
Statistical test	Type	ANCOVA

Study Name		**ATTRACT**
	p-value	NR
Primary outcome	**Name**	**Renal function – $eGFR_{CKD-EPI}$** (Annualised change in eGFR from baseline to month 18) ITT population
	Unit	mL/min/1.73 m²
Effect size	Value: LS Mean ± SEM	Migalastat = [redacted] ERT = [redacted]
	95% CI	Migalastat = [redacted] ERT = [redacted]
Statistical test	Type	ANCOVA
	p-value	NR
Primary outcome	**Name**	**Renal function – $mGFR_{iohexol}$** (Annualised rate of change in $mGFR_{iohexol}$ at 18 months) mITT
	Unit	mL/min/1.73 m²
Effect size	Value: LS Mean ± SEM	Migalastat = -4.35±1.64 ERT = -3.24±2.27
	95% CI	Migalastat = -7.65 to -1.06 ERT = -7.81–1.33
Statistical test	Type	ANCOVA
	p-value	NR
Primary outcome	**Name**	**Renal function – $mGFR_{iohexol}$** (Annualised rate of change in at 18 months) ITT
	Unit	mL/min/1.73 m²
Effect size	Value: LS Mean ± SEM	Migalastat = [redacted] ERT = [redacted]
	95% CI	Migalastat = [redacted] ERT = [redacted]
Statistical test	Type	ANCOVA
	p-value	NR
Secondary outcome	**Name**	**Renal function** – **$eGFR_{MDRD}$,** (Annualised rate of change in at 18 months) mITT
	Unit	mL/min/1.73 m²
Effect size	Value: LS Mean ± SEM	Migalastat = [redacted] ERT = [redacted]
	95% CI	Migalastat = [redacted] ERT = [redacted]
Statistical test	Type	ANCOVA
	p value	NR
Secondary outcome	**Name**	**Composite clinical outcome assessment at 18 months** (mITT)
	Unit	% of patients who had events
Effect size	Value	**Any:** Migalastat = 29%; ERT = 44% **Renal:** Migalastat = 24%; ERT = 33% **Cardiac:** Migalastat = 6%; ERT = 17% **CNS:** Migalastat = 0%; ERT = 6% **Death:** Migalastat = 0%; ERT = 0%
	95% CI	**Any** Migalastat = (14.1, 44.7) ERT = (21.5, 67.4)
Statistical test	Type	ANCOVA
	p-value	NR
Secondary	**Name**	**Cardiac - ECHO findings** – **LVMI** (Change from

Study Name		**ATTRACT**
Outcome		baseline at 18 months) mITT
	Unit	g/m²
Effect size	Value: Mean change	Migalastat = -6.6 ERT = -2.0
	95% CI	Migalastat = -11.0 to -2.2 ERT = -11.0–7.0
Statistical test	Type	ANCOVA
	p-value	NR
Secondary Outcome	**Name**	**Cardiac - ECHO findings** – **LVEF** (Change from baseline at 18 months) mITT
	Unit	Median %
Effect size	Value: Median change	Migalastat = [redacted] ERT = [redacted]
	95% CI	Migalastat = [redacted] ERT = [redacted]
Statistical test	Type	ANCOVA
	p-value	NR
Tertiary outcome	**Name**	**Cardiac - ECHO findings – LVPWT and IVSWT**
	Unit	g/m²
Effect size	Value	[redacted]
	95% CI	NR
Statistical test	Type	ANCOVA
	p value	NR
Secondary outcome	**Name**	**Change from baseline in 24-hour urine protein at 18 months** (mITT population)
	Unit	mg/day
Effect size	Value: Mean ± SD	Migalastat: [redacted] ERT: [redacted]
	95% CI	Migalastat: [redacted] ERT: [redacted]
Statistical test	Type	NR
	p-value	NR
Secondary outcome	**Name**	**24-hour albumin: creatinine ratio, change from baseline at 18 months** (mITT population)
	Unit	mg/nmol
Effect size	Value Mean ± SD	Migalastat: [redacted] ERT: [redacted]
	95% CI	Migalastat: [redacted] ERT: [redacted]
Statistical test	Type	NR
	p-value	NR
Secondary outcome	**Name**	**Plasma lyso-Gb3:** Change from baseline at 18 months (mITT population)
	Unit	Nmol/L
Effect size	Value: Mean ± SD	Migalastat: [redacted] ERT: [redacted]
	95% CI	Migalastat: [redacted] ERT: [redacted]
Statistical test	Type	NR

Study Name		ATTRACT
	p-value	NR
Secondary outcome	**Name**	**WBC alfa-Gal A Activity:** Change from baseline at 18 months (mITT population)
	Unit	nmol/h/mg
Effect size	Value: Mean	Migalastat: [redacted] ERT: [redacted]
	95% CI	Migalastat: [redacted] Placebo: [redacted]
Statistical test	Type	NR
	p-value	NR
Secondary outcome	Name	**PRO - BPI Short Form:** Change From Baseline
	Unit	(Composite Score 0-10)
Effect size	Value: Mean ± SD	Migalastat: [redacted] ERT: [redacted]
	95% CI	Migalastat: [redacted] Placebo: [redacted]
Statistical test	Type	NR
	p-value	NR
Secondary outcome	**Name**	**PRO -** SF-36: Change From Baseline - PCS
	Unit	Physical component score (PCS) 0-100
Effect size	Value: Mean	Migalastat: [redacted] ERT: [redacted]
	95% CI	Migalastat: [redacted] ERT: [redacted]
Statistical test	Type	NR
	p-value	NR
Secondary outcome	**Name**	**PRO -** SF-36: Change From Baseline - MCS
	Unit	Mental component score (PCS) 0-100
Effect size	Value: Mean	Migalastat: [redacted] ERT: [redacted]
	95% CI	Migalastat: [redacted] ERT: [redacted]
Statistical test	Type	NR
	p-value	NR

Abbreviations: ANCOVA = Analysis of covariance; CI = Confidence interval; CNS = Central nervous system; $eGFR_{CKD-EPI}$ = Chronic Kidney Disease Epidemiology Collaboration; $eGFR_{MDRD}$ = Estimated glomerular filtration rate based on MDRD equation; ERT = Enzyme replacement therapy; IVSWT = Intraventricular septal wall thickness; LVPWT = Left ventricular posterior wall thickness; Lyso-Gb3 = Lyso-Globotriaosylsphingosine; $mGFR_{iohexol}$ = Iohexol clearance; NR = Not reported; SEM = Standard error of the mean

Co-primary endpoint results

The co-primary endpoints demonstrated that renal function remained stable over 18 months with migalastat and that migalastat and ERT had comparable effects on renal function (ATTRACT Draft Manuscript). Baseline $eGFR_{CKD-EPI}$ ± SD was 88.7 mL/min/1.73 m^2 ± 20.2 in the migalastat group and 94.7 mL/min/1.73 m^2 ± 20.2 in the ERT group (Amicus Therapeutics, 2016c). As shown in Table C9.14 and Figure C9.7, the prespecified criteria for

comparability of migalastat and ERT were met for both the $mGFR_{iohexol}$ and $eGFR_{CKD-EPI}$ outcomes: the annualised means were within 2.2 mL/min/1.73 m^2/year and the 95% CIs for the means had greater than 50% overlap. That is, patients switched from ERT to migalastat met the prespecified criteria for comparability to patients who remained on ERT.

Table C9.14: Annualised GFR from baseline to month 18

	Population	Migalastat mean±SE (95% CI)	ERT mean±SE (95% CI)	Means within 2.2 mL/min/1.73 m^2/year	95% CI overlap >50%
$eGFR_{CKD-EPI}$	mITT (n=52)	−0.4±0.93 (−2.27, 1.48)	−1.03±1.29 (−3.64, 1.58)	Yes	Yes
	ITT (n=60)	[redacted]	[redacted]	NR	NR
$mGFR_{iohexol}$	mITT (n=52)	−4.35±1.64 (−7.65, −1.06)	−3.24±2.27 (−7.81, 1.33)	Yes	Yes
	ITT (n=60)	[redacted]	[redacted]	NR	NR

CI=confidence interval; $eGFR_{CKD-EPI}$= glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; $eGFR_{MDRD}$=glomerular filtration rate estimated by the Modification of Diet in Renal Disease equation; ERT=enzyme replacement therapy; GFR=glomerular filtration rate; mGFRiohexol= glomerular filtration rate measurement by iohexol clearance; mITT=modified intent to treat; SE=standard error.
Source: (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015d)

Figure C9.7: Annualised change in GFR from baseline to month 18: ANCOVA: LSMs and 95% CIs (mITT population)

ANCOVA=analysis of covariance; CI=confidence interval; eGFR=estimated glomerular filtration rate; $eGFR_{CKD-EPI}$= glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; ERT=enzyme replacement therapy; GFR=glomerular filtration rate; LSM=least square mean; $mGFR_{iohexol=}$ glomerular filtration rate measurement by iohexol clearance.
Source: (ATTRACT Draft Manuscript)

The similarity of the migalastat and ERT treatment effects was also demonstrated in the comparison of the medians and interquartile ranges for each of the co-primary endpoints (Figure C9.8).

Figure C9.8: Annualised change in GFR from baseline to month 18: medians ± interquartile ranges (mITT population)

CI=confidence interval; eGFR=estimated glomerular filtration rate; $eGFR_{CKD-EPI}$= glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; ERT=enzyme replacement therapy; GFR+=glomerular filtration rate; $mGFR_{iohexol=}$ glomerular filtration rate measurement by iohexol clearance; mITT=modified intent to treat.
Source: (ATTRACT Draft Manuscript)

Secondary endpoint results

Secondary renal endpoints

[redacted] (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015d). The annualised means for $eGFR_{MDRD}$ were [redacted]

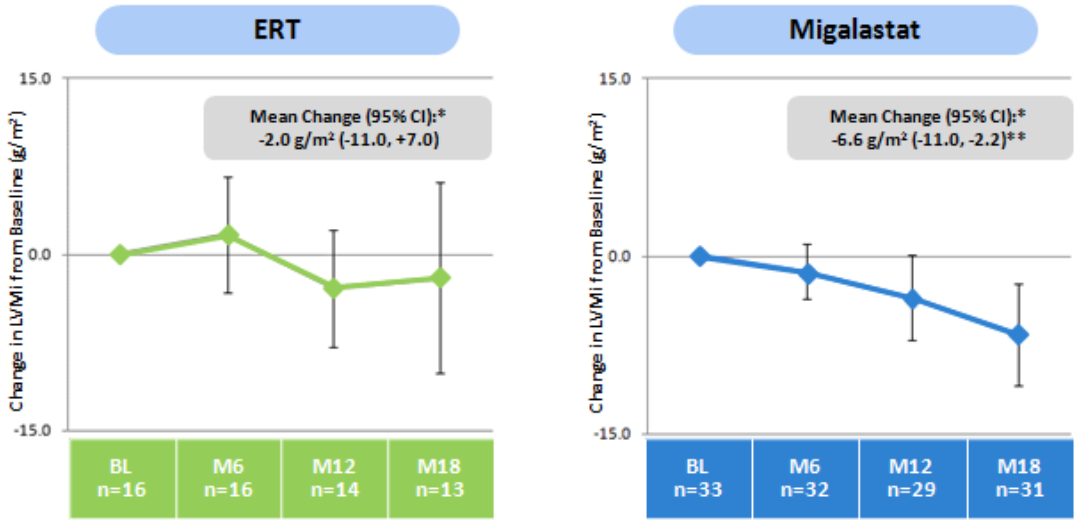
- migalastat mean±SE: [redacted]
- ERT mean±SE: [redacted]

[redacted] in the two treatment groups.

LVMi and other cardiac parameters

LVMi decreased significantly from baseline to 18 months in patients switched from ERT to migalastat (−6.6 g/m^2 [−11, −2.2]); in patients who continued on ERT, the value at 18 months was not significantly different from baseline (−2 g/m^2 [−11, 7]) (Figure C9.9 and Table C9.15). [redacted] (ATTRACT Draft Manuscript).

Figure C9.9: LVMi change (mean and 95% CI) over 18 months with ERT and migalastat



BL=baseline; CI=confidence interval; ERT=enzyme replacement therapy; LVMi=left ventricular mass index.
*Mean change to month 18 in randomised, treated patients with amenable mutations.
**Statistically significant (95% CI does not overlap 0).
Source: (ATTRACT Draft Manuscript)

Table C9.15: LVMi changes on echocardiogram at 18 months (mITT population)

Patients with amenable mutations	Baseline mean g/m^2	Mean change from baseline to month 18 (95% CI)
All (n=33)[a]	95.3 (39%)	−6.6 (−11, −2.2)[b]
Male (n=13)[c]		[redacted]
Female (n=18)[c]		[redacted]
LVH at baseline (n=9 females; 4 males)	116.7 (100%)	−8.4 (−15.69, 2.3)

CI=confidence interval; LVH=left ventricular hypertrophy; LVMi=left ventricular mass index; mITT=modified intent to treat.
[a] Only 33 of the 34 patients in the mITT population had baseline echocardiogram data.
[b] Statistically significant (95% CI does not overlap 0).
[c] Includes only patients who had both a baseline and a month 18 visit.
Source: (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015d)

In terms of other cardiac parameters (Amicus Therapeutics, 2015d):

[redacted]

Composite clinical outcome

The composite outcome included the primary cardiac, renal, and cerebrovascular events associated with morbidity and mortality in Fabry disease (Amicus Therapeutics, 2015c). 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 switched from ERT to migalastat compared to 44% (8/18) of patients who remained on ERT (Table C9.16)(ATTRACT Draft Manuscript). Overall, renal events were the most common, followed by cardiac events. No deaths occurred.

Table C9.16: Composite clinical outcome (mITT population)

Component	Migalastat (n=34), n (%)	ERT (n=18), n (%)
Any event	10 (29%)	8[a] (44%)
Renal event	8 (24%) increased proteinuria (6 patients); decreased GFR (2 patients)	6 (33%) increased proteinuria (4 patients); decreased GFR (3 patients)
Cardiac event	2 (6%) chest pain and VT/chest pain	3 (17%) cardiac failure, dyspnoea, and arrhythmia
Cerebrovascular event	0	1 (6%) TIA
Death	0	0

ERT=enzyme replacement therapy; GFR=glomerular filtration rate; mITT=modified intent to treat; TIA=transient ischemic attack; VT=ventricular tachycardia.
a 2 ERT-experienced patients each had 1 cardiac and 1 renal event.
A patient may have appeared in more than 1 event category but was counted only once in the composite outcome.
Source: (Amicus Therapeutics, 2016c; ATTRACT Draft Manuscript)

Patient-reported outcomes

Results from the SF-36 and the BPI-Pain Severity Component indicate that HRQL and pain levels remained stable for patients switched from ERT to migalastat (Amicus Therapeutics, 2015c).

Scores for the SF-36, which evaluates physical and mental health and functioning, were [redacted] (Table C9.17) (ATTRACT Draft Manuscript).

Table C9.17: SF-36 results

	Baseline, mean±SE		Change from baseline to month 18, mean (95% CI)	
	migalastat (n=34)	ERT (n=16 for PCS; n=17 for MCS)[a]	migalastat (n=31)	ERT (n=16 for PCS; n=17 for MCS)[a]
PCS	[redacted]	[redacted]	[redacted]	[redacted]
MCS	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; ERT=enzyme replacement therapy; MCS=mental component summary; PCS=physical component summary; SE=standard error.
[a] Patients without missing data.
Source: (ATTRACT Draft Manuscript)

Scores on the BPI-Pain Severity Component indicate that patients [redacted] (Table C9.18) (ATTRACT Draft Manuscript).

Table C9.18: BPI-pain severity component results

	Baseline, mean±SE		Mean change from baseline to month 18 (95% CI)	
Treatment	migalastat (n=34)	ERT (n=17)a	migalastat (n=34)	ERT (n=17)[a]
Score	[redacted]	[redacted]	[redacted]	[redacted]

BPI=Brief Pain Inventory; CI=confidence interval; ERT=enzyme replacement therapy; SE=standard error.
[a] Patients without missing data.
Source: (ATTRACT Draft Manuscript).

24-hour urinary protein

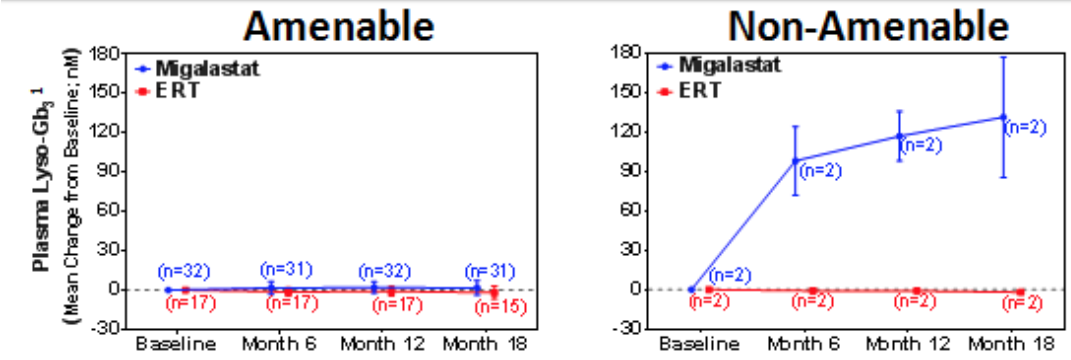
Patients who switched from ERT to migalastat had [redacted] from baseline over 18 months in 24-hour urinary protein compared patients who remained on ERT (Amicus Therapeutics, 2015d):

[redacted]

Plasma lyso-Gb3

In patients with an amenable mutation, lyso-Gb3 levels remained low and stable throughout the 18-month treatment period in both treatment groups (those who were switched from ERT to migalastat and those who remained on ERT) (Figure C9.10). In patients with a non-amenable mutation, lyso-Gb3 levels increased in 2 patients switched from ERT to migalastat, but remained low in two patients who remained on ERT (ATTRACT Draft Manuscript). These findings indicate that migalastat had the same effect as ERT in maintaining low levels of the substrate lyso-Gb3 in patients with amenable mutations. The difference in lyso-Gb3 levels between patients with non-amenable mutations who were switched from ERT to migalastat and those remaining on ERT is consistent with the mechanism of action of migalastat and supports the validity of the Migalastat Amenability Assay in identifying amenable mutations (Amicus Therapeutics, 2015c).

Figure C9.10: Change in lyso-Gb3 during the 18-month treatment period



ERT=enzyme replacement therapy; lyso-Gb3=globotriaosylsphingosine; mITT=modified intent to treat.
Source: (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015d)

PBMC α-Gal A activity

Evaluation of α-Gal A activity in white blood cells (WBCs, specifically, PBMCs) showed results that were consistent with the mechanism of action of migalastat. Normal α-Gal A activity in WBCs is approximately 22 nmol/h/mg (Germain et al., Draft Manuscript). [redacted] (Amicus Therapeutics, 2015d).

FACETS Efficacy Results

Summary

Table C9.19: FACETS Summary of primary and secondary endpoint results (randomised stage, Baseline to Month 6)

Study Name		**FACETS**
Size of study groups (ITT)	Treatment	34
	Control	33
Study duration	Time unit: Months	6
Type of analysis	Intention-to-treat/per protocol	ITT, modified ITT (mITT) indicated for each outcome as appropriate.
Primary outcome	**Name**	**IC GL3 inclusions - Percentage of subjects with a ≥50% reduction in the average number of inclusions at 6 months** (ITT population)
	Unit	%
Effect size	Value: Mean change	Migalastat: 40.6% Placebo: 28.1% Difference: 12.5%
	95% CI	Difference: -13.4, 37.3
Statistical test	Type	Cochran-Mantel-Haenszel test
	p-value	p=0.30
Post hoc analysis	**Name**	**IC GL3 inclusions - Change in mean number of GL-3 inclusions per interstitial capillary at 6 months** ITT population with amenable mutations
	Unit	Mean change
Effect size	Value: Mean change (±SEM)	Migalastat = -0.250 (±0.103) Placebo = +0.071 (±0.13) Difference = -0.3
	95% CI	-0.6, -0.1
Statistical test	Type	Cochran-Mantel-Haenszel test
	p-value	0.008
Secondary outcome	**Name**	**IC GL3 inclusions – Median percent change from baseline at 6 months (**ITT population)
	Unit	%
Effect size	Value: Median change	Migalastat: -40.8% Placebo: -5.6% Difference: 35.2%
	95% CI	NR
Statistical test	Type	ANCOVA model adjusted for baseline value and sex as covariates
	p-value	P=0.097
Tertiary outcome	**Name**	**IC GL3 inclusions - Percent ICs With Zero GL-3 Inclusions (change from baseline to month 6)** ITT population
	Unit	Mean percent change
Effect size	Value: LS Mean	Migalastat = 7.3 (±9.72)

Study Name		FACETS
	change (±SD)	Placebo = 1.3 (±11.75) Difference = 6.0
	95% CI	Difference: 0.2, 11.7
Statistical test	Type	ANCOVA model with covariate adjustment for the baseline value and factors for treatment group, sex, and the treatment by baseline interaction, sex by treatment interaction and sex by baseline interaction
	p-value	0.042
Secondary outcome	**Name**	**Urine GL-3 (Change from baseline to month 6 in substrate)** ITT population with amenable mutations
	Unit	ng/mg creatinine
Effect size	Value: Mean change (±SEM)	Migalastat = –361 (±169) Placebo = –147 (±217)
	95% CI	NR
Statistical test	Type	ANCOVA model with covariate adjustment (ITT population with amenable mutations)
	p-value	NS
Other outcome	**Name**	**Renal function - eGFR$_{MDRD}$ (Mean change from baseline to month 6)** ITT population
	Unit	mL/min/1.73 m²
Effect size	Value: Mean change (±SEM)	Migalastat = [redacted] Placebo = [redacted]
	95% CI	NR
Statistical test	Type	ANCOVA model that included treatment as a factor with the baseline value as a covariate and the treatment by baseline interaction
	p-value	NR
Other outcome	**Name**	**Renal function - eGFR$_{CKD-EPI}$ (Mean change from baseline to month 6)** ITT population
	Unit	mL/min/1.73 m²
Effect size	Value: Mean change (±SEM)	Migalastat = 1.80±1.5 Placebo = –0.3±1.4
	95% CI	NR
Statistical test	Type	ANCOVA model that included treatment as a factor with the baseline value as a covariate and the treatment by baseline interaction.
	p-value	NR
Other outcome	**Name**	**Renal function - mGFR$_{Iohexol}$ (Mean change from baseline to month 6)** ITT population
	Unit	mL/min/1.73 m²
Effect size	Value: Mean change (±SEM)	Migalastat = –1.19±3.4 Placebo = 0.41±2.0
	95% CI	NR
Statistical test	Type	ANCOVA model that included treatment as a factor with the baseline value as a covariate and the treatment by baseline interaction. ITT with amenable mutations
	p-value	NR
Tertiary outcome	**Name**	**Cardiac - Changes from baseline to month 6 in Echo parameters – LV mass index**
	Unit	N/A
Effect size	Value	No statistically significant changes from baseline were observed between placebo and migalastat during the first 6 months of treatment with migalastat.

Study Name		**FACETS**
	95% CI	N/A
Statistical test	Type	NR
	p-value	NR
Tertiary outcome	**Name**	**GSRS** (Mean changes from baseline to month 6) ITT population with amenable mutations
	Unit	Least squares means
Effect size	Value: Mean change in score for all subjects (or subjects with symptoms at baseline as indicated)	**Diarrhoea:** Migalastat = -0.3; Placebo = +0.2 **Reflux:** Migalastat = 0.0; Placebo = +0.2 **Reflux for subjects with symptoms at baseline†:** Migalastat = -0.5; Placebo = +0.3 **Indigestion:** Migalastat = -0.1; Placebo = -0.1 **Constipation:** Migalastat = +0.1; Placebo = +0.2 **Abdominal pain:** Migalastat = 0.0; Placebo = 0.0
	95% CI	NR
Statistical test	Type	ANCOVA. ITT Population With Amenable Mutations
	p-value	**Diarrheal**: $p < 0.05$ *__Reflux__: $p \leq 0.05$ **Reflux for subjects with symptoms at baseline†:** $p = 0.05$
Exploratory outcome	**Name**	**Plasma Lyso-Gb3 - Mean change from baseline to month 6** ITT population with amenable mutations
	Unit	nmol/L
Effect size	Value: Mean change (±SEM)	Migalastat = -11.2 (±4.8) Placebo = 0.58 (±2.4) Difference = -11.4
	95% CI	Difference: -18.7, -4.1
Statistical test	Type	**(Exploratory analysis)** Data were analysed using an ANCOVA model that included treatment as a factor with the baseline value as a covariate and the treatment by baseline interaction
	p-value	0.0033
Tertiary outcome	**Name**	**SF-36v2**
	Unit	Physical component score
Effect size	Value:	Differences between groups or changes from baseline in the SF-36 were not found at 6 months.
	95% CI	NR
Statistical test	Type	NA
	p-value	NA
Tertiary outcome	**Name**	**BPI Short Form**
	Unit	Pain Severity Component
Effect size	Value:	From baseline to month 6, no differences between placebo and migalastat groups were observed.
	95% CI	NR
Statistical test	Type	NA
	p-value	NA
Comments		†Data for this outcome were taken from Schiffman R et al. "Improvement in gastrointestinal symptoms observed in the phase 3 FACETS (AT1001-011) study of migalastat in patients affected with Fabry disease". Paper presented at: Lysosomal Disease Network 2015.

Abbreviations: ANCOVA = Analysis of covariance; CI = Confidence interval; (e)GFR = (estimated) glomerular filtration rate; $eGFR_{CKD-EPI}$ = Chronic Kidney Disease Epidemiology Collaboration; $eGFR_{MDRD}$ = Estimated glomerular filtration rate based on MDRD equation; Gb3 = Globotriaosylceramide; GSRS = Gastrointestinal Symptoms Rating Scale; Lyso-Gb3 = Lyso-Globotriaosylsphingosine; LV = Left ventricular; $mGFR_{iohexol}$ = Iohexol clearance; N/A = Not applicable; NR = Rot reported; NS = Not significant; SEM = Standard error of the mean
Source: (Germain et al., Draft Manuscript; Amicus Therapeutics, 2015d)

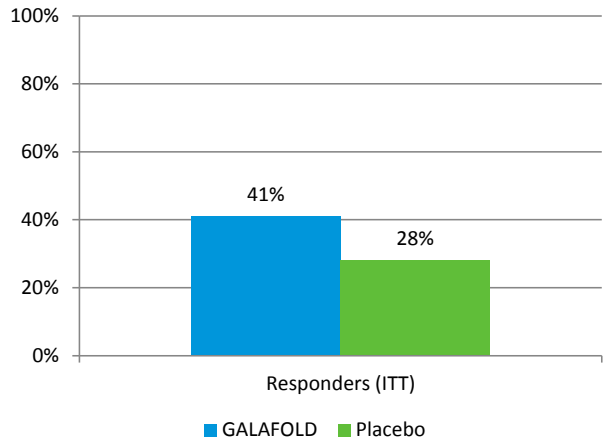
Results

IC GL3 Inclusions

Response to therapy (primary endpoint)

During Stage 1 in the ITT population (i.e., patients with amenable and non-amenable mutations based on the Migalastat Amenability Assay), a reduction in GL3 inclusions per kidney IC of ≥50% was observed in 41% of patients receiving migalastat and 28% of patients receiving placebo, a non-significant difference (*P*=0.30; Figure C9.11). Patients with higher numbers of inclusions at baseline experienced [redacted] (Germain et al., Draft Manuscript).

Figure C9.11: FACETS: percent of patients with ≥50% reduction in kidney IC GL3 inclusions at 6 months (ITT population)



GL3=globotriaosylceramide; IC=interstitial capillary; ITT=intent-to-treat.
Source: (Germain et al., Draft Manuscript)

Additional prespecified kidney IC GL3 inclusion endpoints

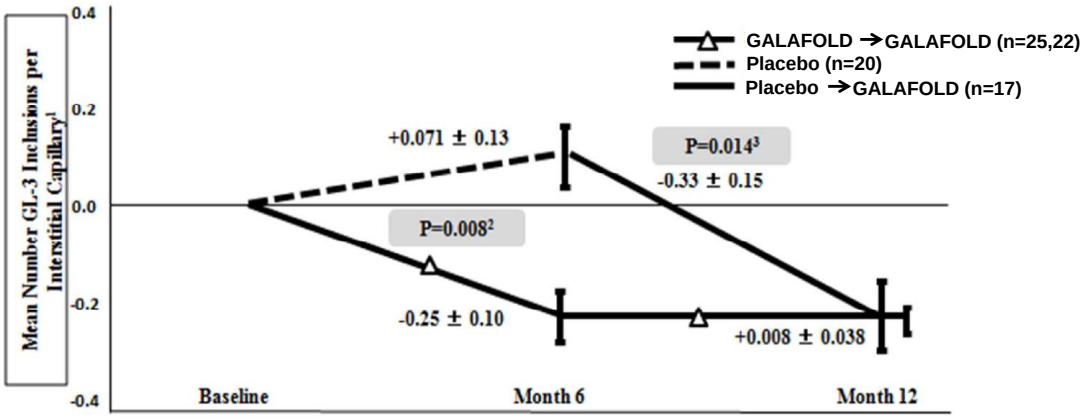
Two other prespecified endpoints in the ITT population also evaluated kidney IC GL3 inclusions: (Germain et al., Draft Manuscript)

- the difference in median percent change in kidney IC GL3 inclusions between migalastat and placebo was [redacted]
- the mean difference in the change in percentage of kidney IC with zero GL3 inclusions was significantly greater with migalastat compared with placebo (7.3% vs. 1.3%, respectively; *P*=0.042)

Post hoc analysis in patients with amenable mutations

However, when a post hoc analysis for Stage 1 was conducted in the population with amenable mutations based on the Migalastat Amenability Assay, there was a significantly larger reduction in GL3 IC inclusions at 6 months for patients receiving migalastat than for patients receiving placebo: −0.250±0.103 vs. 0.071±0.126 inclusions per IC, respectively (*P*=0.008), as shown in Figure C9.12 (Germain et al., Draft Manuscript). There was no difference between migalastat and placebo in patients with non-amenable mutations.

Figure C9.12: Change from baseline in kidney IC GL3 at 6 months in patients with amenable mutations



GL3=globotriaosylceramide; IC=interstitial capillary.
Source: (Germain et al., Draft Manuscript)

Prespecified analyses at 12 months

Evaluation of kidney IC GL3 inclusions in patients with amenable mutations based on the Migalastat Amenability Assay was a prespecified analysis at 12 months (i.e., Stage 2). The reductions observed in the patients with amenable mutations who had received migalastat during Stage 1 were stable through another 6 months of therapy in Stage 2 (the migalastat-migalastat group). The patients who had received placebo in Stage 1 and switched from ERT to migalastat at Month 6 (the placebo-migalastat group) showed significant mean (SE) reduction in kidney IC GL3 inclusions of −0.330 (0.152) (*P*=0.014) following 6 months of treatment with migalastat at Month 12 (Germain et al., Draft Manuscript).

Changes in GL3 inclusions in other kidney cell types were also evaluated at the end of Stage 2. At Month 12, decreases in GL3 inclusions were observed in podocytes in 22% of patients, endothelial cells in 26% of patients, and in mesangial cells in 48% of patients (Germain et al., Draft Manuscript). No increases in any cells were observed.

Changes in renal function

Changes in renal function were evaluated as secondary endpoints. Table C9.20 shows the changes in renal function after 6 months in the migalastat and placebo groups. While the results varied somewhat based on the methodology used to evaluate renal function, these results at 6 months showed [redacted]. Note,

however, that 6 months is generally considered too short a time to show reliable changes in GFR.

Table C9.20: Changes in renal function at 6 months

mL/min/1.73 m^2	Placebo (n=33), mean±SE	migalastat (n=34), mean±SE
$eGFR_{CKD-EPI}$	−0.3±1.4	1.80±1.5
$eGFR_{MDRD}$	[redacted]	[redacted]
$mGFR_{iohexol}$	0.41±2.0	−1.19±3.4

$eGFR_{CKD-EPI}$=glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; eGFRMDRD=glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula; mGFRiohexol=glomerular filtration rate measurement by iohexol clearance; SE=standard error.
Source: (Germain et al., Draft Manuscript; Amicus Therapeutics, 2015c)

Table C9.21 shows the results at Stage 3 in patients with amenable mutations based on the Migalastat Amenability Assay, when the placebo-migalastat group had received 18 months of migalastat therapy, and the migalastat-migalastat group had received 24 months of migalastat therapy. Unlike what is observed in untreated patients, renal function remained stable after 18/24 months of therapy (Schiffmann et al., 2009; Germain et al., Draft Manuscript).

Table C9.21: Renal function after 18/24 months of treatment with migalastat

mL/min/1.73 m^2	Mean±SE (95% CI)	Median
$eGFR_{CKD-EPI}$ (n=41)	−0.30±0.66 (−1.65, 1.04)	0.25
$eGFR_{MDRD}$ (n=41)	[redacted]	[redacted]
$mGFR_{iohexol}$ (n=37)	−1.51±1.33 (−4.20, 1.18)	−1.03

CI=confidence interval; $eGFR_{CKD-EPI}$=glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; $eGFR_{MDRD}$=glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula; $mGFR_{iohexol}$=glomerular filtration rate measurement by iohexol clearance; SE=standard error.
Source: (Germain et al., Draft Manuscript; Amicus Therapeutics, 2015c)

The annualised rate of change in $eGFR_{MDRD}$ in patients receiving migalastat was compared with that of a reference untreated population, which was comprised of 447 patients with Fabry disease from the US, Canada, Czech Republic, Denmark, and the Netherlands who were untreated and followed for a median of 5.6 years (Schiffmann et al., 2009). The baseline characteristics of this untreated population were similar to those of the patients receiving migalastat in terms of age and baseline $eGRF_{MDRD}$ (Germain et al., Draft Manuscript). The mean difference (95% CI) in the annualised rate of change was [redacted] migalastat (Germain et al., Draft Manuscript). The decline in patients treated with migalastat of <1 mL/min/year is within the range of decline due to aging observed in the general population (Hemmelgarn et al., 2006).

Urinary protein [redacted] in patients with amenable mutations after 18/24 months of migalastat treatment (Amicus Therapeutics, 2015a):

- in the migalastat-migalastat group from 1 to 24 months: [redacted]
- in the placebo-migalastat group from 6 to 24 months: [redacted]

Changes in cardiac parameters

In patients with amenable mutations based on the Migalastat Amenability Assay, LVMi was significantly reduced after 18/24 months of migalastat treatment (Table C9.22). A trend toward larger reductions was seen in patients with baseline LVH (Germain et al., Draft

Manuscript). As would be expected after a short time, no changes in LVMi were seen at the end of Stage 1 tertiary endpoints, randomised phase), after 6 months of treatment, between migalastat and placebo (Amicus Therapeutics, 2015c).

Table C9.22: Changes in LVMi in patients with amenable mutations at 18/24 months

Patient group	Baseline mean g/m^2 ± SE	Change from baseline to 18/24 months, mean±SE (95% CI)
All patients with amenable mutations	n=44 96.5 ± 5.0	n=27 −7.69±3.7 (−15.4, −0.0009), *P*<0.05
Patients with amenable mutations with baseline LVH	n=11 138.9 ± 11	n=8 −18.6±8.3 (−38.2, 1.04), *P*=NS

CI=confidence interval; LVH=left ventricular hypertrophy; LVMi=left ventricular mass index; NS=not significant; SE=standard error.
Source: (Germain et al., Draft Manuscript)

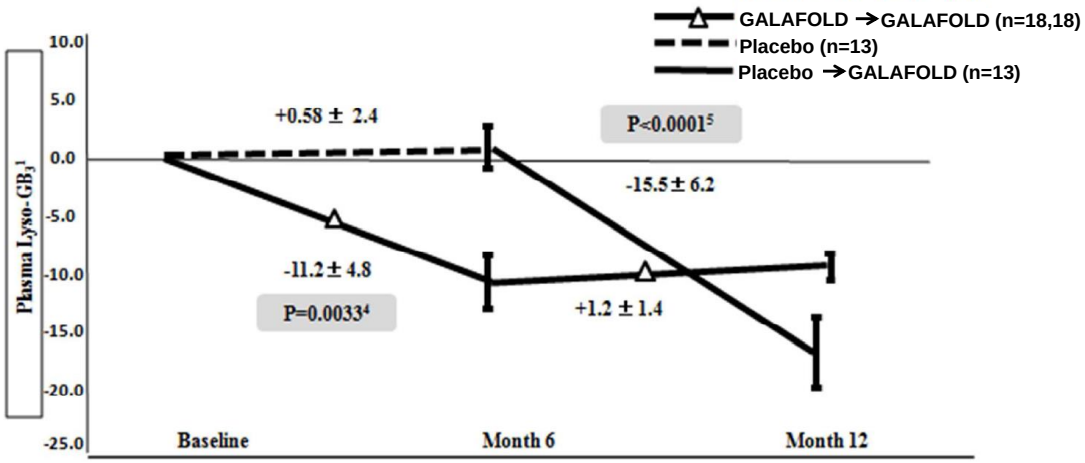
In terms of other cardiac parameters (Amicus Therapeutics, 2015c; Germain et al., Draft Manuscript):

- Intraventricular septal wall thickness decreased by 5.2% from baseline to 18/24 months and the change was correlated with the change in LVMi (R^2=0.26, *P*=0.006)
- LV posterior wall thickness remained stable
- LVEF and fractional shortening were generally normal at baseline and remained stable
- Systolic and diastolic function grades were [redacted]

Changes in plasma lyso-Gb3

In patients with amenable mutations based on the Migalastat Amenability Assay, plasma lyso-Gb3 (an exploratory endpoint) was decreased significantly at 6 months in patients who had received migalastat vs. those who had received placebo (−11.2 vs. 0.58, *P*=0.0033) (Figure C9.13). The reduction remained stable over an additional 6 months of treatment with migalastat; at 12 months, patients in the placebo-migalastat group showed a reduction (Germain et al., Draft Manuscript).

Figure C9.13: Change from baseline in plasma lyso-Gb3 in patients with amenable mutations



Lyso-Gb3=globotriaosylsphingosine.
Source: (Germain et al., Draft Manuscript)

Change in urinary GL3

Overall, there was high variability in urine GL3 values. Analyses of the change from Baseline (secondary endpoint, Stage 1) for the ITT Population and the change from Baseline (Stage 2) for patients with amenable mutations are shown in Table C9.23.

Table C9.23: Changes in urinary GL3

Measure	Change from baseline in urinary GL3 (ng/mg creatinine)
Stage 1, mean±SE	
migalastat	−361±169
Placebo	−147±217
Stage 2, patients with amenable mutations, mean	
migalastat-migalastat	[redacted]
Placebo-migalastat	[redacted]

GL3=globotriaosylceramide; SE=standard error.
Source: (Germain et al., Draft Manuscript)

24-Hour Urine

24-hour urine protein, albumin, and creatinine were assessed as secondary endpoints in Stage 1. Urine protein and albumin levels [redacted]

PBMC α-Gal A activity

The activity of α-Gal A was measured for male patients (tertiary endpoint). In a stage 1 (6 months) post hoc analysis of males with amenable mutations based on the Migalastat Amenability Assay, [redacted]

[redacted] (Amicus Therapeutics, 2015a).

PRO results

Changes in the SF-36 after 18/24 months of migalastat therapy (in patients with amenable mutations) are summarised in Table C9.24 (Germain et al., Draft Manuscript). As shown below, significant improvements were seen in the vitality and general health domains from baseline; the values for the other health domains remained stable.

Table C9.24: SF-36 results at 24 months in patients with amenable mutations

SF-36 domain[a]	Change from baseline after 18/24 months of migalastat, mean (95% CI)
Vitality domain	4.0 (0.1, 8.0)[b]
General health domain	4.5 (0.2, 8.9)[b]

CI=confidence interval; SF-36=Short Form-36 Health Survey.
[a] The other domains of the SF-36 remained stable.
[b] Statistically significant based on 95% CIs.
Source: (Germain et al., Draft Manuscript)

GI symptoms are common in patients with Fabry disease and have a substantial negative impact on patients, producing pain and distress, and affecting participation in activities (Germain, 2010; MacDermot et al., 2001b). The GSRS evaluates the level of discomfort due to 15 GI symptoms. On the GSRS, at 6 months, more patients receiving migalastat had improvement in the diarrhoea domain compared with placebo (38% vs. 9%), and there was a significant difference in scores for this domain between the 2 groups (−0.3 for migalastat vs. 0.2 for placebo, *P*<0.05)(Germain et al., Draft Manuscript; Amicus Therapeutics, 2015d). In a post hoc analysis of patients who had symptoms at baseline, there was also a significant difference in the scores for reflux at 6 months favouring migalastat (−0.5 for migalastat vs. 0.3 for placebo, P<0.05). After 18/24 months of treatment, patients receiving migalastat had significant improvement from baseline in the diarrhoea and indigestion domains (both in all patients and in those who had symptoms at baseline), and there was a trend for improvement in the reflux and constipation domains (Table C9.25). Symptoms of abdominal pain remained stable.

Table C9.25: GSRS results at 24 months

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

CI=confidence interval; GSRS=Gastrointestinal Symptom Rating Scale.
[a] Statistically significant based on 95% CIs.
Source: (Germain et al., Draft Manuscript; Amicus Therapeutics, 2015a)

Changes in BPI severity component scores did not differ between groups from baseline to Month 6 and from Month 6 to Month 24 (Germain et al., Draft Manuscript).

Open-label, long-term extension studies

Outcomes after 18/24 months of treatment with migalastat

Some preliminary data are available for patients who entered AT1001-041 from FACETS: patients originally randomised to migalastat in FACETS had received 24 months of treatment with migalastat, while patients originally randomised to placebo in FACETS and who were switched to migalastat when they began the open-label extension had received 18 months of treatment with migalastat (Amicus Therapeutics, 2015c). As noted previously, the majority of patients originally enrolled in AT1001-041 are continuing treatment in AT1001-042.

Renal function at an average of 36 months

As described above, renal function remained stable in patients in FACETS who had received migalastat for 24 months (patients initially randomised to migalastat and continuing in the 6-month and 12-month OLEs) or 18 months (patients initially randomised to placebo and continuing in the 6-month and 12-month OLEs). Renal function continued to remain stable in patients who continued in AT1001-041 for an average of 36 months (range 18 months to 54 months). The mean±SEM annualised rate of change in $eGFR_{CKD-EPI}$ was (Amicus Therapeutics, 2015c; Germain et al., Draft Manuscript):

- −0.3±0.66 mL/min/1.73 m^2/year after up to 24 months in FACETS
- [redacted] mL/min/1.73 m^2/year for an average of 36 months (range 18 to 54 months) in patients who continued in AT1001-041

Note that this decline of [redacted] min/1.73 m^2/year compares favourably with the long-term decline experienced by untreated patients with Fabry disease (−2.2 to −12.2 mL/min/1.73 m^2/year) and is within the range of decline seen in healthy adults with aging (−1 mL/min/1.73 m^2/year) (Schiffmann et al., 2009; Stevens et al., 2006; West et al., 2009; Branton et al., 2002; Schwarting et al., 2006; Hemmelgarn et al., 2006).

Cardiac parameters at an average of 36 months

As previously noted, in FACETS and its OLEs, patients treated with migalastat for 18 or 24 months showed a decrease in LVMi (Germain et al., Draft Manuscript). In patients who continued in AT1001-041 and had migalastat treatment for 30 or 36 months, there were further reductions in LVMi, and the decrease was greater in patients with LVH at baseline (Amicus Therapeutics, 2015c). Table C9.26 summarises these data.

Table C9.26: LVMi change from baseline in FACETS and AT1001-041 with migalastat treatment

Parameter	All patients (n=48)	LVH at baseline (n=11)
FACETS		
N	27	8
Mean change from baseline at month 18/24 (95% CI), g/m^2	−7.7 (−15.4, −0.01)	−18.6 (−38.2, 1.0)
AT1001-041		
N	[redacted]	[redacted]
Mean change from baseline at month 30/36 (95% CI), g/m^2	[redacted]	[redacted]

CI=confidence interval; LVH=left ventricular hypertrophy.
Source: (Amicus Therapeutics, 2015c)

ATTRACT: 30 Months Data

The following section outlines recent 30-month data from the extension phase of ATTRACT (18 months randomised treatment plus 12 months open-label migalastat treatment).

The 30-month analyses include patients with amenable mutations (based on the Migalastat Amenability Assay) and baseline/post-baseline measures of eGFR and mGFR (renal analyses) or LVMi (ECHO analyses).

Renal function

30-month findings show that stabilisation of renal function continued with longer migalastat treatment. The 30-month mean (95% CI) annualised rate of change from Baseline in $eGFR_{CKD\text{-}EPI}$ was -1.7 mL/min/1.73 m^2 (-2.7, -0.8) and change from baseline in $mGFR_{iohexol}$ was -2.7 (-4.8, -0.7) (Bichet et al., 2016). The annualised rates of change in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ for migalastat are comparable to those previously reported in patients receiving ERT for 18 months: -1.0 (-3.6, 1.6) and -3.2 (-7.8, 1.3), respectively.

Cardiac hypertrophy

The mean (95% CI) annualised change from baseline in LVMi for all 31 patients and for the 11 patients with LVH at baseline were -3.8 (-8.9, 1.3) and -10.0 (-16.6, -3.3), indicating long-term clinical benefit of migalastat treatment on cardiac hypertrophy. In patients with LVH at baseline, the reduction to month 30 for migalastat was statistically significant based on the 95% CIs (Bichet et al., 2016).

These results show persistent clinical benefit in patients treated longer-term with migalastat.

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

As discussed in Section 9.4.1, the preliminary HEK assay was used to determine amenability for enrolment into the Phase 3 studies. The assay was modified and validated following the initiation of the Phase 3 studies and termed the Migalastat Amenability Assay.

In ATTRACT, a modified intent-to-treat (mITT) population was specified in the statistical analysis plan (SAP). This population (n=52) includes all randomised subjects with mutations amenable to migalastat in the GLP HEK essay that received at least one dose of study medication and have both the baseline and at post baseline efficacy measure of $mGFR_{iohexol}$ and a post-baseline measure of $eGFR_{CKD\text{-}EPI}$.

Similarly, in FACETS, analysis of the population with amenable mutations has been presented alongside the ITT. This population was defined prior to unblinding of the study. In FACETS 50 of 67 randomised patients were found to have amenable mutations with the Migalastat Amenability Assay.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

See sections 9.1 to 9.6.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

Adverse events

ATTRACT

Migalastat appeared to be well-tolerated during the 18-month treatment period. No clinically relevant effects of migalastat were observed on safety parameters, nor were there any differences between patients switched from ERT to migalastat and those who remained on ERT in terms of vital signs, physical findings, ECG parameters, or laboratory tests (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015b).

Discontinuation

During the 18-month randomised treatment period, no patient discontinued treatment due to a treatment-emergent adverse event (TEAE) (ATTRACT Draft Manuscript). As noted previously, 3 patients initially randomised to continue on ERT withdrew consent before receiving any study medication and were excluded from the analyses (ATTRACT Draft Manuscript).

During the OLE period, 2 patients discontinued, both due to AEs judged possibly related to migalastat treatment (Amicus Therapeutics, 2015b). One patient in the migalastat-migalastat group was withdrawn with a serious adverse event (SAE) of mild proteinuria, and was found to be pregnant. A patient in the ERT-migalastat group withdrew due to TEAEs of mild diarrhoea and mild vomiting.

Adverse events

The proportion of patients with a TEAE was similar for the migalastat (94%) and ERT (95%) groups (ATTRACT Draft Manuscript). In general, TEAEs were mild to moderate in severity and were judged unrelated to the study drug (Amicus Therapeutics, 2015b). The most frequent (≥25%) TEAEs reported in the migalastat group [redacted] (Table C9.27) (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015b). SAEs, all judged unrelated to study treatment, were reported in [redacted] of patients in the ERT group and in [redacted] of patients in the migalastat group. There were no deaths in the study (ATTRACT Draft Manuscript).

Table C9.27: Summary of TEAEs and SAEs (safety population)

	Migalastat (n=36)	ERT (n=21)
Proportion with TEAE, %	[redacted]	[redacted]
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]
URTI	[redacted]	[redacted]
UTI	[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]
SAEs	[redacted]	[redacted]

SAE=serious adverse event; TEAE=treatment emergent adverse event; URTI=upper respiratory tract infection; UTI=urinary tract infection.
Source: (ATTRACT Draft Manuscript; Amicus Therapeutics, 2015b, 2015d)

FACETS

Discontinuation

No patients discontinued migalastat due to TEAEs. There were 2 discontinuations due to SAEs, both considered unrelated to migalastat (Germain et al., Draft Manuscript).

Adverse events

TEAEs are summarised in Table C9.28. During Stage 1, headache and nasopharyngitis were reported at greater frequency for migalastat than placebo. During Stage 2, the most frequently reported TEAEs were headache and procedural pain. For Stage 3, the most frequently reported TEAEs were proteinuria, headache, and bronchitis. Most TEAEs were mild or moderate in severity (Germain et al., Draft Manuscript).

Table C9.28: Summary of TEAEs and SAEs

AE, %	Migalastat (n=34)	Placebo (n=33)
Stage 1		
Patients with any TEAE, %	[redacted]	[redacted]
Patients with any SAE, n	[redacted]	[redacted]
TEAEs ≥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)
	All patients receiving migalastat	
Stage 2		
Patients with any SAE, n	[redacted]	
TEAEs ≥10%, n (%)		
Headache	9 (14)	
Procedural pain	7 (11)	
Nasopharyngitis	5 (8)	
Arthralgia	[redacted]	
Tachycardia	3 (5)	
Stage 3		
Patients with any SAE, n	[redacted]	
TEAEs ≥10%, n (%)		
Proteinuria	9 (16)	
Headache	6 (11)	
Bronchitis	6 (11)	

SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Source: (Germain et al., Draft Manuscript; Amicus Therapeutics, 2015a; Barlow et al., 2014)

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

The following summary is based on the entire clinical development programme for migalastat (Amicus Therapeutics, 2015b). The migalastat clinical development programme included diverse populations [males and females, healthy volunteers, volunteers with renal impairment, patients with Fabry disease, and elderly subjects (> 65 years of age)] and a range of doses and regimens (50 mg – 2000 mg).

In the clinical development programme, 386 subjects have been exposed to migalastat. Of these, 168 patients with Fabry disease have been treated with migalastat in Phase 2 and Phase 3. One hundred and nineteen (119) patients have been treated for at least 1 year. The longest patient exposure to date is 8.8 years, and is ongoing.

- No safety issues were identified with short or long-term treatment. Treatment with migalastat HCl up to 2000 mg was found to be generally safe and well tolerated.
- TEAEs reported with the use of migalastat were mostly mild or moderate in nature, and required no intervention or were readily managed in standard clinical practice.
- The overall frequency of TEAEs was generally similar for migalastat and ERT [[redacted]]. The frequency and profile of TEAEs was similar between migalastat and placebo

treatment, and reflected adverse events that are typical in clinical trials and that are associated with underlying Fabry disease. There were no adverse event trends attributable to migalastat. The most common TEAE in the phase 3 studies was [redacted]

- There were no deaths related to migalastat. There were 2 deaths unrelated to migalastat (one from breast cancer, one from unknown cause in a patient with history of heart disease, obesity, and diabetes).
- In ATTRACT, serious AEs were [redacted] migalastat group ([redacted] of patients) compared with the ERT group ([redacted]), and were considered unrelated to migalastat.
- Only 2 patients experienced SAEs considered possibly related to migalastat (fatigue and paraesthesia in 1 patient, and moderate proteinuria in 1 patient, FACETS).
- There were few discontinuations due to TEAEs, and most were related to underlying Fabry disease co-morbidities.
- [redacted].

It is advised to periodically monitor renal function, echocardiographic parameters and biochemical markers (every 6 months) in patients initiated on or switched to migalastat. It is expected that migalastat will not be recommended for use in patients with severe renal insufficiency defined as estimated GFR less than 30 mL/min/1.73m^2 (Amicus Therapeutics, 2016c).

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

A systematic literature review (SLR) was carried out to identify randomised controlled trials (RCTs) of treatments in this therapeutic area (described in Section 9.1 and Section 17), and subsequently the feasibility of performing a network meta-analysis (NMA) of these studies was assessed. A key conclusion of this feasibility assessment was that no credible NMA could be conducted for migalastat in patients with Fabry disease for key outcomes.

The detailed findings of the feasibility assessment are presented in a separate report (Amicus Therapeutics, 2016b). A total of eight RCTs were deemed relevant for inclusion in the feasibility evaluation (Banikazemi et al., 2007; Eng et al., 2001; Hughes et al., 2008, 2013b; Schiffmann et al., 2001; Vedder et al., 2007b; Germain et al., Draft Manuscript; ATTRACT Draft Manuscript). Two were subsequently excluded (one was a dose comparison study, the other did not include a licensed dose regimen). Although hypothetical networks could be formed using the remaining six studies, when outcomes were assessed for similarity between trials, no credible network remained for analysis of any outcome of interest (Table C9.29). In

addition, there would also have been sufficient heterogeneity in patient characteristics between the studies to seriously undermine the results of any NMA of the outcomes (Table C9.30).

In conclusion, a network meta-analysis of RCTs of treatments for patients with Fabry disease is unworkable owing to multiple concerns about the feasibility of conducting such an analysis and/or the dubious credibility of any results it might produce. In particular, such issues are related to the heterogeneity of the outcomes reported in the studies and some key differences across trials in the patient baseline characteristics that would, ultimately, mean that a network meta-analysis would be biased by factors unrelated to any true clinical differences between these treatments.

Table C9.29: Key Highlights from the Feasibility Assessment by Outcome

Outcome	Feasibility and Credibility of any Potential NMA
GL3 levels in kidney samples	• 2 of 6 trials reported on change in kidney GL3 content (in nmol/L) but they differed in the techniques used to measure Gb3 (i.e., BLISS vs. HPLC), and this could reduce the credibility of any NMA for this outcome.
GL3 levels in urine samples	• 4 of 6 trials reported on GL3 levels in urine samples. However, migalastat trials provided data in different units (i.e., ng/mg vs. nmol/g in the other studies) and, therefore, could not be quantitatively synthesised for this outcome with the other trials in the evidence network. • Also, measurement of urinary GL3 levels was discontinued in the ATTRACT trial in light of problems experienced in the earlier FACETS trial during collection and handling of urine to assess this outcome. • The three trials other than the ATTRACT trial each used different techniques to measure GL3 (i.e., LC-MS/MS, HPLC, NR).
Kidney function	• 3 of 6 trials reported on GFR but it is not appropriate to pool data on this outcome across studies because GFR in Fabry disease is typically skewed in line with certain patient characteristics (i.e., age and disease progression).
Cardiac function	• 3 of 6 trials (FACETS, ATTRACT, and TKT 0075) reported on change in LVMi from baseline to end of treatment; however, in general, the literature suggests that a six-month period (as reported in these studies) may not be sufficient to observe any clinically relevant treatment effect, although some data indicate otherwise.
Progression-free survival (occurrence of renal, cardiac, neurological, and cerebrovascular events)	• 2 of 6 trials reported on renal, cardiac, neurological and cerebrovascular events, both as a composite and as individual outcomes. However, in the ATTRACT trial these outcomes were reported as the number of patients experiencing the event, whereas the AGAL-008-00 trial reported only time to such event, making an NMA based on these two studies unfeasible. • In addition, there was heterogeneity between studies in the definitions used for renal events.
Mortality	• The FACETS and ATTRACT trials had no reported death events within the study period and, therefore, this outcome could not be analysed quantitatively through an NMA.
Symptoms of Fabry disease (including pain)	• 3 of 6 trials reported on BPI-SF, but the time points for assessing this outcome varied (being 24 weeks, 6 months, and 18 months, respectively), making an NMA of this outcome unfeasible.
Health-related quality of life	• Only the migalastat trials provided quantitative data for the SF-36 and, therefore, this outcome could not be assessed across treatments by an NMA.
Adverse effects of treatment	• An NMA of AEs was not feasible because of the differences in how such events were reported from trial to trial (a common feature of studies on rare diseases) and the fact that most trials did not report what definition of AEs they used.

Abbreviations: AE, adverse event; BPI-SF, Brief Pain Inventory Short Form; BLISS, Barisoni Lipid Inclusion Scoring System; CI, confidence interval; GL3, globotriaosylceramide; GFR, glomerular filtration rate; HPLC, high-performance liquid chromatography; HR, hazard ratio; LC-MS/MS, liquid chromatography-mass spectrometry/mass spectrometry; LVMi, left ventricular mass index; NR, not reported; SF-36, Short Form-36

Table C9.30: Key Highlights from the Feasibility Assessment by Population Characteristic

Population Characteristic	Feasibility and Credibility of Any Potential NMA
Gender	• In the FACETS and ATTRACT trials the proportion of male participants was 35% and 44%, respectively, compared with at least 87% in other trials. • These differences are important as clinical symptoms and signs of Fabry disease generally manifest earlier and are more severe in males than in females.
Time Since Diagnosis	• The FACETS trial reported a mean time since diagnosis of 6.3 years compared with the ATTRACT trial and one other study in the evidence network (Schiffmann, 2001), that reported approximately 10 to 13 years. • Patients with a shorter disease history may respond differently (i.e., better) to treatment compared with patients with a longer duration of illness.
Disease severity	• Although there is some suggestion that baseline GFR was similar among four trials that reported on this characteristic, published literature indicates that Fabry disease encompasses a wide spectrum of disease severity ranging from so called 'classic' to 'later-onset' forms; this makes any attempt to have a similar population across trials based on disease severity challenging in Fabry disease.

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The efficacy of migalastat for the treatment of patients with Fabry disease has been demonstrated in one active-controlled (ATTRACT) and one placebo-controlled (FACETS) Phase 3 study and their open label extensions.

Progressive renal dysfunction is a major aspect of Fabry disease and is associated with the complications of end-stage renal disease, dialysis, and renal transplantation (Germain, 2010; Waldek et al., 2009; Pisani et al., 2014). In Fabry disease, slowing the progressive decline in renal function is a key treatment objective. In ATTRACT and FACETS, migalastat stabilised renal function (Germain et al., Draft Manuscript; ATTRACT Draft Manuscript):

- In ATTRACT, the effects of migalastat on renal function in patients switched from ERT to migalastat were comparable to the effects of ERT in patients who remained on ERT.
- In FACETS, migalastat stabilised renal function in ERT-naive patients for up to 3 years. This is in contrast to the progressive decline that occurs in untreated patients.

Cardiac complications are the main cause of death in patients with Fabry disease (Wilcox et al., 2008; Nagueh, 2014). Left ventricular hypertrophy (LVH) is the most common cardiac manifestation in these patients and it is an important risk factor for cardiac events (Nagueh, 2014). Migalastat therapy produced significant improvement in left ventricular mass index (LVMi), a key measure of left ventricular (LV) mass. (Germain et al., Draft Manuscript; ATTRACT Draft Manuscript):

- In ATTRACT at 18 months, patients switched from ERT to migalastat had significantly decreased LVMi from baseline ($P<0.05$), while LVMi was not significantly changed from baseline in patients remaining on ERT.
- Migalastat also significantly decreased LVMi in the FACETS trial in ERT-naïve patients at 18/24 months, and the decrease continued in the open-label extension at up to 3 years.

Furthermore, rates of renal, cardiovascular, and cerebrovascular events experienced by patients switched from ERT to migalastat in ATTRACT compared favourably with those experienced by patients who remained on ERT (29% vs. 44%, respectively) (ATTRACT Draft Manuscript). Data for the individual components of the composite endpoint were:

- Renal: 24% with migalastat vs. 33% with continued ERT
- Cardiac: 6% with migalastat vs. 17% with continued ERT
- Cerebrovascular: 0% with migalastat vs. 6% with continued ERT
- Death: 0% for both migalastat and continued ERT

Other symptoms of Fabry disease can also negatively impact the lives of patients. In FACETS in ERT-naïve patients, migalastat significantly improved GI symptoms such as diarrhoea and indigestion (Amicus Therapeutics, 2015a). In addition, HRQL remained stable in patients switched from ERT to migalastat in ATTRACT, and improved in ERT-naïve patients in FACETS (Amicus Therapeutics, 2015a, 2015d).

Consistent with its mechanism of action, migalastat effectively reduces tissue accumulation and circulating levels of disease substrate:

- In patients switched from ERT (ATTRACT), plasma lyso-Gb3 remained low and stable for 18 months when patients were switched from ERT to migalastat.
- In ERT-naïve patients (FACETS), migalastat significantly reduced plasma lyso-Gb3 (P=0.0033) and interstitial capillary GL3 inclusions (P=0.008). Patients who switched from placebo to migalastat at 6 months for the open-label extension also showed significant decreases in plasma lyso-Gb3 (P<0.0001) and interstitial capillary GL3 inclusions (P=0.014).
- Patients receiving migalastat also had significantly qualitative reductions in GL3 levels in multiple types of renal cells over 12 months.

Treatment with migalastat resulted in an increase in endogenous α-Gal A activity (ATTRACT Draft Manuscript; Germain et al., Draft Manuscript):

- In ATTRACT, patients had a baseline α-Gal A activity of <3% of normal. By month 18, α-Gal A activity had risen by a median of 6.6 nmol/mg/h with migalastat, vs. 0.04 nmol/mg/hr in patients remaining on ERT.
- In FACETS, patients had a baseline α-Gal A activity of <3% (<1% in 44% of patients) of normal. At 6 months, patients receiving migalastat had a mean increase in endogenous α-Gal A activity of 2.4 nmol/mg/h with no change in patients who had received placebo.
- Information from the clinical literature has shown that an increase of only 1% to 5% of normal α-Gal A activity in vivo is sufficient to produce a clinically meaningful result (Desnick, 2004).

Migalastat is well-tolerated, with headache the only adverse event (AE) ≥10% in clinical trials. In ATTRACT, the frequency of headache was similar in patients who were switched to migalastat and those who remained on ERT. In addition:

- Migalastat is not associated with the IARs that commonly occur with ERT because it is an oral agent.
- There is negligible risk of immunogenicity with migalastat because it is a small molecule.
- There is no risk of infections associated with vascular access because migalastat is an oral agent.

Migalastat provides consistent increases in α-Gal A throughout the body because it has a high bioavailability and wide tissue distribution. There is a low risk for interactions with other drugs because migalastat is largely (55%) eliminated unchanged in the urine (as measured via urine metabolite analysis), and has little interaction with P-glycoprotein or the cytochrome P450 system.

Migalastat has a once-every-other day oral administration regimen that does not interfere with the lives of patients or caregivers.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Migalastat has been studied in a robust monotherapy program that includes four phase 3 studies (2 pivotal and 2 long-term ongoing extensions). The patient population in the international phase 3 studies exhibited the full spectrum of severity of clinical manifestations associated with Fabry disease and are reflective of the expected treatment population in the UK.

The phase 3 data provide consistent evidence of a clinical benefit with migalastat that is comparable to ERT based on multiple surrogate outcome measures as well as an indication of an increased benefit on cardiac function based on the LVMi. Furthermore, migalastat compared favourably to ERT in the composite outcome that included renal, cardiovascular, and cerebrovascular events.

A standard noninferiority analysis comparing migalastat and ERT on the co-primary endpoints was not possible due to the small sample size. Therefore, prespecified criteria were developed in conjunction with the EMA to define comparability of GFR results for migalastat and ERT. Due to differing administration methods, ATTRACT was an open-label study.

The FACETS study did not meet its primary endpoint in the ITT population. Limitations were identified with the primary endpoint responder analysis. Because a number of subjects had low values at Baseline, small changes in IC GL3 inclusions would result in large changes when viewed as a percent change from Baseline. The Stage 1 data revealed an imbalance in the mean baseline level of IC GL3 inclusions between the placebo and migalastat groups (about 50% higher in the migalastat group). Consequently, small decreases in IC GL3 inclusions in subjects with low baseline IC GL3 inclusions could meet the 50% reduction from Baseline (Visit 1) more easily than subjects with higher baseline IC GL3 inclusions. As a result, the responder analyses did not accurately reflect the effect of migalastat on IC GL3 inclusions, and the placebo group had a higher than expected “response” rate.

Scientifically, the change from Baseline (i.e., quantitative difference) in IC GL3 inclusions more accurately assesses the biological effect of migalastat on IC GL3 inclusions than the responder analysis. This was reflected in the trend favouring migalastat seen in the Stage 1 secondary endpoint: percent change from Baseline in IC GL3 inclusions. On this basis, the key analyses of IC GL3 inclusions in the Stage 2 SAP used the data as a continuous variable in an adjusted analysis of covariance (ANCOVA) and a mixed effects model for repeated measures (MMRM).

The Migalastat Amenability Assay was validated during the conduct of the Phase 3 studies. Therefore in FACETS the primary analyses of Stage 1 (the 6 month randomised phase) included all randomised subjects. A post-hoc analysis was undertaken for patients with amenable mutations based on the validated assay. The efficacy analyses in the Stage 2 SAP of FACETS were focused on the subjects with amenable mutations based on the validated assay. In ATTRACT, a pre-specified mITT analysis included only those patients with amenable mutations based on the validated assay.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence base is relevant to the scope in both terms of study population and the specified outcome measures. The evidence from ATTRACT is considered to be the most relevant data according the scope, since it provides a direct comparison with the relevant comparators, agalsidase alfa and agalsidase beta (ERT). In ATTRACT, patients enrolled had been treated with agalsidase alfa or agalsidase beta and if randomised to the ERT arm continued to receive at least 80% of the currently labelled dose and regimen during the treatment period. This is considered to be an appropriate comparator group since biochemical studies have shown no functional difference between the two protein preparations (Genzyme Therapeutics, 2014; Shire, 2006; Lee et al., 2003) and they are considered to be comparable in terms of their efficacy and side effect profile (see Section 8).

In patients with Fabry disease, slowing the decline in renal function is a key treatment objective. Studies assessing GFR in untreated and ERT-treated patients (Germain et al., 2007; Warnock et al., 2012; Wanner et al., 2010; Schiffmann et al., 2009; Schwarting et al., 2006) show that annualised rates of decline in GFR are in the range of -2.2 to -12.7 ml/min/m^2 in untreated patients and -2.2 to -2.9 ml/min/m^2 in ERT-treated Fabry patients. Based on these data, derived from a large number of studies, the effect of ERT is to slow the decline in GFR in Fabry disease; but improvement (increase) in GFR is not expected with ERT treatment. Migalastat treatment was associated with stabilisation of renal function, which is clinically meaningful, since the effect of ERT is stabilising or slowing decline in GFR. The effects of migalastat and ERT on renal function were comparable, and longer-term stabilisation of renal function by migalastat has been shown over 3 years of treatment.

The natural history of LVMi and cardiac hypertrophy in untreated Fabry patients regardless of phenotype (Patel et al., 2015) is a progressive increase in LVMi between +4.07 and +8.0 g/m^2/year (Kampmann et al., 2008; Wyatt et al., 2012; Germain et al., 2013). LVH is the greatest risk factor for cardiac events in Fabry disease (Patel et al., 2011), and any reduction in LVH has been shown to have a positive impact on cardiovascular morbidity and mortality in hypertensive heart disease (Pokharel and Bella, 2013). Migalastat leads to reduction, and not just stabilisation, of LVMi. Since LVMi increases over time in Fabry disease in the absence of treatment, the reduction of LVMi in both Phase 3 studies is a clinically relevant treatment effect of migalastat, including larger effects in patients with LVH at baseline. Patients treated with migalastat in both Phase 3 studies and in the open-label extension exhibited statistically significant decreases in LVMi, with a clinically relevant improvement in particular in patients with existing cardiac hypertrophy. This effect has shown to be persistent over 3 years of treatment.

Gastrointestinal symptoms are a prominent and clinically important manifestation of Fabry disease. Patients commonly suffer from debilitating gastrointestinal symptoms, including diarrhoea, nausea, faecal incontinence, vomiting, abdominal pain, and constipation (Banikazemi et al., 2005; Hoffmann et al., 2007). Results from 366 patients with Fabry disease in the Fabry Outcomes Survey revealed that gastrointestinal symptoms were reported in 55% of males and 50% of females (Mehta, Ricci et al. 2004). Gastrointestinal manifestations of Fabry disease often have profound negative effects on social and economic functioning and quality of life in male and female patients (Gold, Pastores et al. 2002). Thus,

improving gastrointestinal symptoms is clinically relevant in the daily life of patients with Fabry disease. In FACETS, gastrointestinal symptoms improved in 3 of 5 domains (diarrhoea, reflux, indigestion) assessed by the GSRS in patients with amenable mutations treated with migalastat. The minimal clinically important difference (MCID) for the diarrhoea domain in the GSRS is an improvement from baseline ≥0.4 units (Chan et al., 2006). While calculated in a non-Fabry population, it is likely that this MCID also represents a clinically relevant improvement in the Fabry population. Based on the MCID, 69% of the migalastat-treated patients experienced a clinically relevant change versus 11% of the placebo-treated patients (p=0.012).

In ATTRACT, migalastat compared favourably to ERT in the incidence of Fabry-associated clinical events (renal, cardiac, and cerebrovascular), which are the main sources of morbidity and mortality in patients with this disease.

Phase 3 studies have demonstrated the efficacy and safety of migalastat in both ERT-naive and ERT-experienced patients with amenable mutations. In patients with amenable mutations (estimated to be between 30–50% of currently diagnosed patients with Fabry disease), migalastat, administered orally every other day, has clear advantages over ERT (Amicus Therapeutics, 2015c):

- With regard to the burden of treatment, an orally administered medication would be a significant benefit to patients and their families over ERT infusions.
- Patients receiving migalastat do not have IARs that occur commonly with ERT.
- As a small molecule, migalastat does not have the risk of immunogenicity that is present with ERT.
- Oral treatment eliminates the risk of infections associated with vascular access that is required for ERT administration.
- As a small molecule, migalastat has broad tissue distribution. It is anticipated that this characteristic may offer enhancement of α-Gal A activity levels in multiple organs (e.g., heart) and tissues. Migalastat also has distribution across the blood-brain barrier.
- Every-other-day oral migalastat provides more consistent chaperoning of endogenous α-Gal A to the lysosome that is closer to natural enzyme trafficking than every-other-week infusions of manufactured ERT.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The proposed indication for migalastat is for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (Amicus Therapeutics, 2016c).

The patients in the phase 3 studies for migalastat are reflective of the population of patients with Fabry disease that will be treated in practice, and are similar in the extent and types of organ system involvement and in the level of renal impairment to the patients included in ERT registries and the pivotal ERT trials. Patients in the migalastat clinical trials exhibited the full spectrum of severity of clinical manifestations associated with Fabry disease. The majority of

patients in both trials had multi-organ disease at baseline ([redacted] of patients with amenable mutations in ATTRACT and 60% of those in FACETS had mutations associated with classic Fabry disease.

Migalastat is an important addition to the therapeutic options available for patients with Fabry disease, who would otherwise be treated with ERT. The most recent recommendations on initiation of ERT are as follows (Biegstraaten et al., 2015):

- For classically affected males, ERT is recommended as soon as there are early clinical signs of kidney, heart or brain involvement, but may be considered in patients of ≥16 years in the absence of clinical signs or symptoms of organ involvement.
- Classically affected females and males with non-classic Fabry disease should be treated as soon as there are early clinical signs of kidney, heart or brain involvement.
- Treatment may be considered in females with non-classic Fabry disease with early clinical signs that are considered to be due to Fabry disease.
- Treatment should not be withheld from patients with severe renal insufficiency (GFR < 45 ml/min/1.73 m^2) and from those on dialysis or with cognitive decline, but carefully considered on an individual basis.

In clinical practice in the UK it is expected that migalastat will be used in a subgroup of patients with Fabry disease that are eligible for ERT. Migalstat is expected to be indicated for patients with Fabry disease who have amenable mutations and who are 16 years or older. In addition it is expected that migalastat will not be recommended for use in patients with ESRD.

Enrolment criteria for ATTRACT and FACETS did not include any restrictions relating to disease severity or organ involvement, other than exclusion of patients with ESRD. However, patients in ATTRACT were already on ERT and the majority of patients in both studies had multi-organ disease and the trial populations are thought to be reflective of the population that will be treated in clinical practice.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

In clinical practice, and as per the expected indication for migalastat, only patients with amenable mutations will be eligible for treatment. As stated above, it is expected that the criteria for initiating therapy with ERT will apply to migalastat.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

Fabry symptoms and severity

Early clinical manifestations of Fabry disease, which usually appear in childhood or adolescence, include pain, skin abnormalities, and gastrointestinal symptoms:

- Pain is an early, and the most debilitating, symptom and can be a lingering source of complaint in both men and women (Gold et al., 2002; Żuraw et al., 2011; MacDermot et al., 2001b; Street et al., 2006). The disease specific symptom acroparesthesia is a predictor of decreased quality of life. In a study of 53 men not receiving ERT, pain had a substantial association with all eight SF-36 domains. A one point increment in the 'bothered by' pain results in a decrement of 6 and 17 points across the eight SF-36 HRQL domains (Gold et al., 2002). Similarly in two studies of women with Fabry disease, pain was one of the symptoms that had a high impact on HRQL (Street et al., 2006; Wang et al., 2007). Patients indicated that the pain interfered the most with their mood, ability to work, enjoyment of life, and general activity (Wang et al., 2007).
- Skin abnormalities also impact on HRQL. Anhidrosis (abnormal lack of sweat in response to heat) is a predictor of decreased quality of life. Anhidrosis is associated with a significant decrement in physical function, general health and vitality (Gold et al., 2002).
- Patients with Fabry disease experience significant GI symptoms and report recurrent bouts of abdominal pain, nausea, vomiting, diarrhoea, constipation, and feeling of abdominal distension as well as superficial abdominal skin tenderness (MacDermot et al., 2001b, 2001a; Street et al., 2006; Wang et al., 2007). GI symptoms tended to occur after meals and often patients were afraid to eat as a result of these symptoms. Hoffmann et al. specifically investigated GI complaints amongst male and female patients with Fabry disease using the EQ-5D and found patients with GI complaints had a lower EQ-5D score than those without GI complaints (Hoffmann et al., 2007).

Other symptoms that affect HRQL such as tinnitus, hearing loss, recurrent vertigo, headache, fatigue, depression, and a diminished level of physical activity appear most commonly in the second decade of life.

As the disease progresses, there is increasing renal, cardiac and vascular involvement, including renal insufficiency, heart disease, and stroke, which represent the major source of disease-related morbidity. As in the general population, stroke, cardiac problems and renal disease lead to substantial decrement in HRQL (Gold et al., 2002; Miners et al., 2002; Street et al., 2006). In one study of patients with Fabry disease who were naïve to ERT, significant differences for all SF-36 domain scores except for Mental Health were reported among patients with an eGFR of >60 ml/min/1.73 m^2, patients with an eGFR of <60 ml/min/1,73 m^2 and patients receiving renal replacement therapy (Wagner et al., 2014). Patients with Fabry disease who suffer a stroke may experience significant reduction in HRQL related to aphasia, dysarthria, hemiplegia and other motor impairments, chronic urinary tract infection and depression. In men with Fabry disease, having a heart complication was associated with a decrease in HRQL scores anywhere between 17 and 34 points on the SF-36 (Gold et al., 2002).

Studies have shown a correlation between disease severity (as measured by the MSSI) and HRQL (Duning et al., 2009; Deegan et al., 2006), which was supported by Rombach et al. (2013a) who defined four disease states; asymptomatic, acroparasthesia/ symptomatic, single

complication and multiple complications, and found lower EQ-5D utility scores with more severe disease.

Treatment administration

As discussed in detail in Section 7.2 and Section 8, the biweekly IV infusions of ERT can interfere with the lives of patients and their caregivers, and are associated with a risk of infusion-associated reactions and infections (Ramaswami, 2011; Cousins et al., 2008; Milligan et al., 2006; Borgwardt et al., 2013; Parini et al., 2010).

[redacted]

In addition, in a DCE conducted to understand treatment preferences in Fabry disease, the UK general population was asked about their preferences in terms of mode of administration of treatment, frequency of reaction to the treatment, frequency of headache as a side effect and the long-term risk of developing antibodies (see Section 10.1.9). All of these attributes were found to be statistically significant predictors of choice (Lloyd et al., 2016). Participants expressed a strong preference for an oral treatment over an infusion treatment. Participants also preferred to avoid treatments with headaches and treatments with some form of treatment reaction (such as flu like symptoms). This analysis illustrates the strong preferences regarding treatment choice in Fabry disease.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

Over the natural course of disease progression, HRQL in patients with Fabry disease deteriorates. As described above, as disease progresses patients experience an increasing number of symptoms that may contribute to decreased HRQL.

Observations of the natural history of Fabry disease, indicate that neuropathic pain is the single major source of morbidity during the first two decades of life. Although chronic pain may continue into the later decades of life, the clinical picture in adulthood is often dominated by renal and cardiac problems, and ultimately neurologic disease. As discussed above, other symptoms that may affect HRQL such as tinnitus, hearing loss, recurrent vertigo, headache, fatigue, depression, and a diminished level of physical activity appear most commonly in the second decade of life. In one study, excessive fatigue was reported by adults but was not present in children (MacDermot et al., 2001b).

In line with the relationship between disease severity and HRQL, higher age has been associated with lower HRQL (Arends et al., 2015). HRQL in males starts to decline at younger age than in female patients as shown by a Fabry Registry (a Genzyme sponsored post-marketing drug registry) study in which males between 18 and 25 years of age had

significantly lower SF-36 scores in 6 of 8 subdomains whilst females had normal scores in all but the subscales Bodily Pain and General Health (Wilcox et al., 2008). Above the age of 25, both males and females showed impaired QoL in the subdomains Physical Functioning, Bodily Pain, General Health and Vitality. In the study by Gold et al. (Gold et al., 2002), patients older than 40 had significantly lower physical function which was considered by the authors to be likely due to the progression of renal disease as well as the cumulative increase in patients suffering from stroke and heart problems. All other SF-36 domains indicated a trend in decreased HRQL with age, with substantial differences in the means between age groups, although these did not reach statistical significance. In another study (untreated males, n=38), EQ-5D utility scores were significantly associated with age (p=0.006) and the rate at which scores declined was significantly higher for individuals with Fabry disease compared with individuals in the general population (Miners et al., 2002).

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-consequence analysis.
- Results with confidence intervals.

In both the FACETS and ATTRACT study, quality of life was assessed using the SF-36v2™ Health Survey and the BPI Short-Form Pain Severity Component every 6 months. SF-36 results were reported as physical and mental component scores (0-100) and BPI results were reported as a 1-10 score.

Whilst it is possible to generate utilities from the SF-36, either by mapping to the EQ-5D or valuation using SF-6D, the data required to classify the trial patients into the health states for the chosen model structure (see Section 12.1.3) was not collected in the studies. Therefore, it is not possible to generate health-state utility data from the clinical trial that exactly matches the health state definitions used by Rombach et al (2013a). In addition, patients with ESRD were excluded from the ATTRACT study (Table C9.4) so no data for patients with ESRD would be available from the clinical study to inform the cost-consequence analysis.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

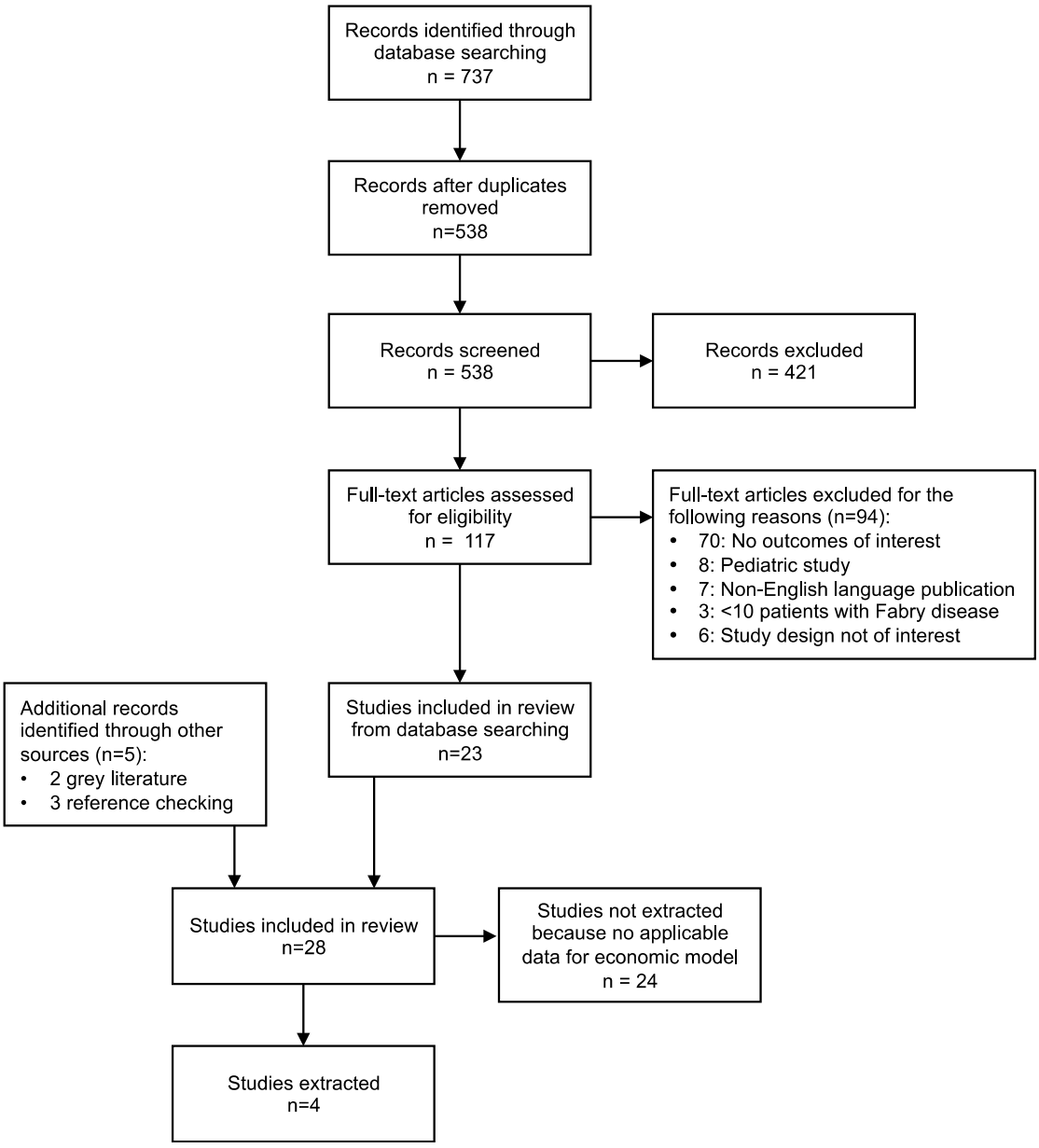
No mapping was used to transform the quality-of-life data collected in clinical trials.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic search of any HRQL measured in patients with Fabry disease was conducted, as detailed in section 17.1. The corresponding PRISMA diagram is presented as Figure C10.1.

Figure C10.1: PRISMA diagram for HRQL systematic review



10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.

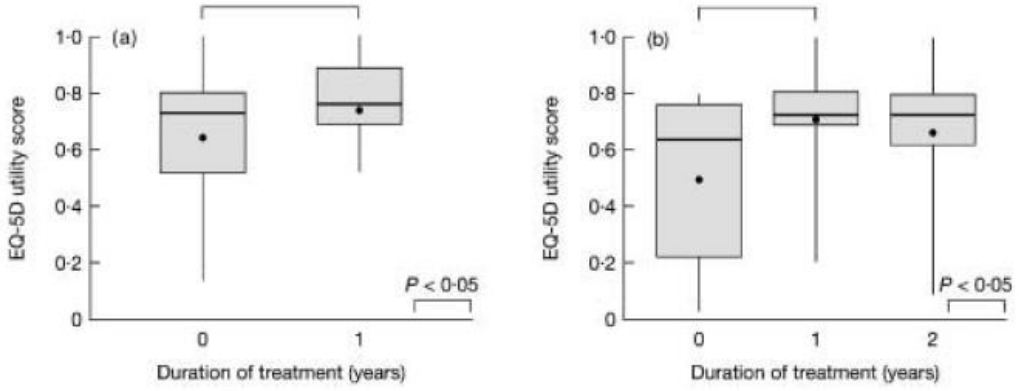
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

The following studies were included in the review but did not provide adequate data that could be used to inform the economic model either because utilities were not presented or could not be calculated, or because data was reported for the total population rather than by health state:

1. Baehner et al (2003) measured the SF-36 in 15 German patients receiving agalsidase alfa and reported by total and domain scores (no utilities).
2. Beck et al (2004) reported EQ-5D utilities for European patients by duration of treatment with agalsidase alfa (see Figure C10.2) but not by health state.
3. Bouwman et al (2011) measured the SF-36 in 28 Dutch adults with Fabry disease. No data were collected according to disease severity or health state (only gender).
4. Cole et al (2007) measured the Centre for Epidemiological Studies – Depression scale (CES-D) in 184 UK patients, which cannot be mapped to utilities.
5. Gibas et al (2006) assessed HRQL using a disease-specific questionnaire in 79 Canadian patients with Fabry disease, from which utilities cannot be obtained.
6. Gupta et al (2005) used the BPI to assess pain in patients in the US with Fabry disease, from which utilities cannot be obtained.
7. Guffon et al (2004) generated a brief questionnaire of 8 questions to assess the effect of ERT on the symptoms of 17 patients with Fabry disease, from which utilities cannot be generated.
8. Hilz et al (2004) reported the Total Symptom Score (TSS) to assess severity of neuropathic pain, before and after treatment with agalsidase beta in 22 US patients with Fabry disease, from which utilities cannot be generated.
9. Hughes et al (Hughes et al., 2011) compared HRQL in women and men with Fabry disease using the EQ-5D. No data were collected according to disease severity or health state.
10. Hoffmann et al (2007) reported HRQL as assessed by the EQ-5D in 108 Fabry patients with and without GI symptoms. The model does not include GI symptoms in any of the disease states therefore this data was not incorporated. No other data were collected according to disease severity or health state.

11. Hoffmann et al (Hoffmann et al., 2005) reported HRQL as assessed by the EQ-5D, prior to and following ERT. No data were collected according to disease severity or health state.
12. Laney et al (2010) measured the Achenbach System of Empirically Based Assessment (ASEBA), Adult Self Report (ASR), Adult Behavior Checklist (ABCL), SF-36, Mainz Severity Score (MSS) and BPI in 30 US patient with Fabry disease. Results were not presented by health state.
13. Lohle et al (2015) assessed HRQL in Fabry patients compared to matched controls using the SF-36, EQ-5D and BPI. No data were collected according to disease severity or health state.
14. Low et al (2007) assessed HRQL in Australian Fabry patients using the SF-36, EQ-5D and a specifically developed questionnaire. No data were collected according to disease severity or health state.
15. Mehta et al (2009) assessed HRQL using the EQ-5D, in patients in the Fabry Outcome Survey database, before and after ERT. No data were collected according to disease severity or health state.
16. Milligan et al (2006) assessed patient satisfaction with ERT using a questionnaire developed specifically for the study, from which utilities cannot be generated.
17. Oliveira et al (2012) measured the SF-36 in 14 Brazilian patients with Fabry disease. No SF-36 data were collected according to disease severity or health state.
18. Schermuly et al (2011) measured the SF-36 in 25 German adults with Fabry disease. No data were collected according to disease severity or health state.
19. Street et al (2006) reported the SF-36 and a Fabry disease-specific questionnaire of their own design. No data were collected according to disease severity or health state.
20. Watt et al (2010) used the SF-36 to measure HRQL in Fabry Registry patients on ERT in a longitudinal analysis. No data were collected according to disease severity or health state.
21. Wilcox et al (2008) assessed HRQL using the SF-36 in 558 Fabry patients enrolled in the Fabry Registry. No data were collected according to disease severity or health state.
22. Wyatt et al (2012) used the SF-36, EQ-5D and the PedsQL to measure the effect of ERT on HRQL in patients attending a National Specialised Commissioning Group-designated lysosomal storage disorder (LSD) treatment centre in England. No data were collected according to disease severity or health states.
23. Zuraw et al (2011) assessed HRQL and the effect of ERT and gender on HRQL among Polish Fabry patients in a cross-sectional study using the SF-36 and the EQ-5D and a Fabry-specific questionnaire. No data were collected according to disease severity or health state.
24. Wang et al (2007) assessed HRQL in 44 female patients from a US centre using the SF-36 and the BPI. No data were collected according to disease severity or health state.

Figure C10.2: EQ-5D utilities reported by Beck et al (2004) for patients followed up for (a) 1 year [n=59] and (b) 2 years [n=28]



As a result of the above 19 studies not reporting HRQL suitable for the model (cannot be mapped to EQ-5D or not reported by disease status or health state), only four studies were extracted in Table C10.1.

Table C10.1: HRQL studies found in the systematic review relevant to the economic model

Gold et al (2002)	
Population in which health effects were measured	Patients registered with the Fabry support and information group, living in the US and having confirmed or assumed Fabry disease, or having close contact with a patient with Fabry disease (such as a mother). No age restriction applied so may include patients aged under 16 (and therefore not applicable to this evaluation). Included 9 patients under the age of 20 but exact age not specified. Surveys were completed by all patients but detailed data is only reported for males.
Information on recruitment	Each one of the patients/caregivers was invited to complete the survey and return it by mail or to call a Freephone number to complete the survey over the telephone or obtain further information on the study.
Interventions and comparators	Not reported
Sample size	200
Response rates	43% (n=85) of which 26.4% were proxy responses primarily completed by the parents/guardian of children with Fabry disease.
Description of health states	In order to understand the impact of age, comorbidities and symptom levels on HRQL, a series of simple linear regressions were estimated for each of the eight domains of the SF-36 using each co-morbidity, age group and symptom. Due to the limited number of subjects in this study, contrasts were only possible for the following categories: renal disease, stroke, and heart disease.
Adverse events	Not reported
Appropriateness of health states given condition and treatment pathway	The results provide the impact on QoL of having renal disease, stroke, heart problems and heart complications. They do not provide absolute utility values for each of these health states but do provide the decrement with such complications. This data can therefore be used to approximate the utility of patients in more severe health states (renal disease, heart disease and stroke) as long as the baseline quality of life for less severe

	symptoms can be sourced from elsewhere.
Method of elicitation	SF-36
Method of valuation	Not conducted in study but could utilities be generated via the SF-6D.
Mapping	The mapping from SF-36 to the EQ-5D by Rowen et al (2009) can be used to approximate EQ-5D utilities from the data in the publication, but this is not specific to a Fabry disease population. There are no published mappings in Fabry disease.
Uncertainty around values	The results by health state are only presented as a simple linear regression and are therefore subject to a high degree of uncertainty. Given the limited sample size, the authors stated they were unable to use age co-morbidities and symptom level as covariates – thus focused on a more descriptive assessment of the HRQL of Fabry patients and did not conduct any hypothesis testing, per se. Less than half the covariates were statistically significant so should be interpreted with caution.
Consistency with reference case	Not EQ-5D which is the NICE preferred measure of HRQL, not a UK cohort and there are no published mappings in Fabry disease.
Results with confidence intervals	Results from Table 4 of the publication are presented below. Simple linear regressions are presented for each domain which is on a 1-100 scale, such that the first value can be interpreted as: if a patients has renal disease, they will have a score 19 points lower on the Physical function domain than a patient without renal disease. The simple generalised least squares model of all dimensions from SF-36 to the EQ-5D by Rowen et al (2009) was used to approximate EQ-5D utilities. Results for the symptoms severity and frequency are not presented here, as they cannot be easily interpreted; these attributes were scored on a 1-5 scale rather than binary responses.

	Physical function	Role physical	Bodily pain	General health	Vitality	Social function	Role emotional	Mental health	**Estimated EQ-5D**
Renal	19.06	23.62	9.63	11.22	4.04	9.01	7.14	-1.91	**-0.10**
Stroke	33.81	33.33	27.31	14.26	13.72	13.62	29.56	17.07	**-0.25**
Heart problem	16.62	21.59	5.74	22.26	12.56	13.07	7.14	2.31	**-0.11**
Heart complications	33.28	34.15	22.22	26.41	28.20	25.17	34.24	17.15	**-0.26**

Wagner et al (2014)	
Population in which health effects were measured	Patients with Fabry disease over the age of 16 that first attended the centre from June 2001 to August 2009.
Information on recruitment	In regular visits to the Comprehensive Heart Failure Center (University of Würzburg), patients were enrolled in an international observational cohort study if they provided written informed consent.
Interventions and comparators	All patients were naïve to therapy at first visit and 45% of patients were initiated on ERT within the first 3 months of first visit.
Sample size	96 patients but complete HRQL data missing in 9 patients so 86 patients data were analysed.
Response rates	Not reported
Description of health states	• eGFR ≥60 ml/min/1.73 m^2 (stage 1 and 2 chronic kidney disease)

	• eGFR <60 ml/min/1.73 m^2 (stage 3 and 4 chronic kidney disease) • Renal replacement therapy (dialysis or kidney transplantation)
Adverse events	Not reported
Appropriateness of health states given condition and treatment pathway	This study only captures one aspect of Fabry disease but does provide estimates of how quality of life varies by kidney disease stage rather than many studies which just provide estimates of HRQL with our without renal complications.
Method of elicitation	SF-36
Method of valuation	Not conducted.
Mapping	The mapping from SF-36 to the EQ-5D by Rowen et al (2009) can be used to approximate EQ-5D utilities from the data in the publication, but this is not specific to a Fabry disease population.
Uncertainty around values	Interquartile ranges (IQR) and medians are presented.
Consistency with reference case	Not EQ-5D which is the NICE preferred measure of HRQL, not a UK cohort and there are no published mappings in Fabry disease
Results with confidence intervals	Results are presented as medians (IQR) below.

	eGFR >60 ml/min/1.73 m^2 n = 66	eGFR <60 ml/min/1.73 m^2 n = 10	RRT (dialysis or KTx) n = 9
Physical functioning	85 (65; 100)	52.5 (25; 75)	50 (30; 55)
Role physical	100 (25; 100)	37.5 (0; 100)	0 (0; 37.5)
Bodily pain	68 (51; 100)	41 (41; 64)	22 (12; 51)
General health	57 (46; 79.5)	45 (35; 52)	25 (17; 40)
Vitality	52.5 (32.5; 65)	40 (30; 50)	30 (5; 30)
Social functioning	87.5 (62.5; 100)	75 (50; 100)	25 (25; 50)
Role emotional	100 (66.7; 100)	100 (0; 100)	33.3 (0; 33.3)
Mental health	66 (52; 80)	64 (52; 76)	44 (28; 60)
Physical component summary	49.8 (37.7; 54.7)	35.9 (24.8; 44.4)	29.4 (25.0; 35.5)
Mental component summary	47.1 (41.5; 54.5)	49.8 (35.4; 56.3)	30.1 (24.5; 34.9)

Rombach et al (2013a)	
Population in which health effects were measured	116 adults and 26 children (age range: 5–78 years) with a confirmed diagnosis of Fabry disease. Two cohorts were defined: an (ERT) cohort and a natural history (NH) cohort. Patients were classified as typical or atypical patients on the basis of phenotype, genotype and biochemical data. Both cohorts mainly consisted of patients with a classic phenotype. A minority consisted of atypical patients with the R112H and P60L substitutions or patients with intermediate levels of plasma lysoGb3.
Information on recruitment	Prospective data were collected from ERT treated patients (n=75) in the Dutch Fabry cohort between 1999 and 2010. NH cohort data were derived from medical records of Fabry patients who had a history of complications before ERT was available or from Fabry patients with an indication for ERT who remained untreated after ERT became available.
Interventions and	ERT: agalsidase alfa 0.2 mg/kg/2 weeks or agalsidase beta at a dose of

<table>
<tr><td>comparators</td><td>0.2 mg/kg/2 weeks or 1.0 mg/kg/2 weeks.
NH: untreated</td></tr>
<tr><td>Sample size</td><td>ERT cohort: n=75, NH cohort: n=142</td></tr>
<tr><td>Response rates</td><td>Not reported</td></tr>
<tr><td>Description of health states</td><td>Other data captured in the publication is detailed for very comprehensive health states but given low patient numbers in the more progressive disease states, results were clustered by four states:
Asymptomatic
Acroparesthesia (neuropathic pain in the extremities) / symptomatic (clinical signs and/or symptoms of left ventricular hypertrophy, chronic kidney disease stages 1-4, or white matter lesions)
Single complication, defined as end stage renal disease (chronic kidney disease stage 5, dialysis or kidney transplant), cardiac complication(s) (atrial fibrillation, any other rhythm disturbance needing hospitalization, pacemaker or implantable cardiac defibrillator (ICD) implantation, cardiac congestion for which hospital admittance was needed, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft), or cerebrovascular accident (stroke, as diagnosed by a neurologist)
Multiple complications</td></tr>
<tr><td>Adverse events</td><td>Not reported</td></tr>
<tr><td>Appropriateness of health states given condition and treatment pathway</td><td>The health states are appropriate and are reflective of stages through which patients progress in the natural course of disease. The disease states are simplifications as in clinical practice there may be expected to be some overlap, for example patients may experience pain, whilst having evidence for a degree of cardiac, and/or renal involvement.</td></tr>
<tr><td>Method of elicitation</td><td>Health status profiles were gathered quarterly with the EQ-5D quality of life questionnaire</td></tr>
<tr><td>Method of valuation</td><td>Time trade-off based health utilities were averaged per patient per disease state and, subsequently, per disease state over patients. The publication references Dolan et al (1997) for this valuation and thus it is assumed that this Dutch cohort was valued using UK preferences.</td></tr>
<tr><td>Uncertainty around values</td><td>95% confidence intervals are shown below.</td></tr>
<tr><td>Consistency with reference case</td><td>Given the data has been collected using the EQ-5D and valued using the UK general population preferences, it is consistent with the reference case.</td></tr>
<tr><td>Results with confidence intervals</td><td>
<table>
<tr><th></th><th>N*</th><th>Mean health utility</th><th>95% CI</th></tr>
<tr><td>Asymptomatic</td><td>19</td><td>0.874</td><td>0.804-0.934</td></tr>
<tr><td>Acroparesthesia/ Symptomatic</td><td>55</td><td>0.762</td><td>0.699-0.822</td></tr>
<tr><td>Single complication</td><td>18</td><td>0.744</td><td>0.658-0.821</td></tr>
<tr><td>Multiple complications</td><td>5</td><td>0.584</td><td>0.378-0.790</td></tr>
<tr><td>Total</td><td>97</td><td>0.722</td><td>0.729-0.815</td></tr>
</table>
*Patients may contribute to more than one disease state.
</td></tr>
<tr><td colspan="2">Miners et al (2002)</td></tr>
<tr><td>Population in which health</td><td>Patients in the UK with Fabry disease, mean age 37.2 years.</td></tr>
</table>

effects were measured	
Information on recruitment	The AFD (Anderson Fabry disease) register, which is a regularly updated UK database established in 1985, was used to identify individuals with Fabry disease in the UK (including Northern Ireland). At the time of the study, the database contained information on 63 families and 79 affected males with Fabry disease living in the UK. Questionnaires were posted to the patients along with a prepaid reply envelope. Individuals who did not reply after 4 weeks were sent a single reminder.
Interventions and comparators	No treatment intervention
Sample size	59 patients
Response rates	38 patients returned all 3 questionnaires
Description of health states	Individuals were asked to state whether or not they had ever experienced GI symptoms, chest pains, stroke, palpitations, loss of vision or swollen ankles. Participants were also asked to state whether they were currently receiving haemodialysis and awaiting a transplant and whether they had undergone a renal transplant.
Adverse events	Not reported
Appropriateness of health states given condition and treatment pathway	Absolute results were not presented by health state but regression analyses were presented with the following symptoms as covariates: • Heart symptoms • Gastrointestinal (GI) symptoms • End-stage renal failure • Stroke As per Rombach et al (2013a), the health states are appropriate and are reflective of stages through which patients progress in the natural course of disease. This study differs to Rombach et al in that it also explicitly captures GI symptoms.
Method of elicitation	Three questionnaires were used: the SF-36, the EQ-5D, and a specially devised AFD-specific questionnaire.
Method of valuation	Valuation of the SF-36 was not conducted and is not possible for the AFD-specific questionnaire. The valuation of the EQ-5D data was not specified but it is assumed that the UK tariff was used.
Mapping	Not conducted.
Uncertainty around values	95% confidence intervals are shown below.
Consistency with reference case	The collection of HRQL in UK patients with Fabry disease and values using the UK tariff is consistent with the reference case. However, scores for each health state were not reported but rather regression analyses from which the decrement in utility by symptom can be approximated.
Results with confidence intervals	Given the EQ-5D results are more consistent with the reference case than the SF-36 or disease-specific questionnaire, only the EQ-5D results for the patients with Fabry disease are summarised here.

Domain	AFD N = 38 (%)
Mobility	
No problems	19 (50.0)
Some problems	18 (47.4)
Confined to bed	1 (2.6)
Self-care	
No problems	28 (73.7)
Some problems	9 (23.7)
Unable to	1 (2.6)
Usual activities	
No problems	17 (44.7)
Some problems	20 (52.7)
Unable to	1 (2.6)
Pain	
None	10 (26.3)
Moderate	21 (55.3)
Extreme	7 (18.4)
Anxiety/depression	
None	19 (50.0)
Moderate	14 (36.8)
Extreme	5 (13.2)
Mean $EQ_{utility}$ (SD)	0.56 (0.35)

Relationship between HRQL, symptoms and age using univariate regression analysis:

	EQ-5D utility	
	β	p-value
Age	-0.017	0.006
Heart symptoms	-0.20	0.12
GI symptoms	-0.07	0.54
ESRD	-0.25	0.12
Stroke	-0.28	0.07

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Utilities were not generated from the quality of life data collected in the clinical trials.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

The adverse events experienced by patients with Fabry disease on treatment with migalastat are generally mild to moderate (Amicus Therapeutics, 2015b) with influenza then gastritis having the greatest impact on HRQL. Patients treated with ERT can experience headache; IARs including fever, fatigue and nausea; itching; oedema; redness at the site of the infusion;

and neutralising antibody formation. The HRQL impact of these events are detailed in Section 10.1.9.

Quality-of-life data used in cost-consequences analysis

10.1.9 Please summarise the values you have chosen for your cost-consequence analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Utility values reported in Rombach et al., 2013 are used, which were calculated from EQ-5D (EuroQol-5 dimension) questionnaires completed by the majority of the patients in their Fabry disease cohort. The associated time trade-off-based health utilities were averaged per patient per disease state using the UK tariff (Dolan, 1997). The publication does not differentiate utilities by complication type or by 2nd or 3rd complication due to low numbers in more progressive health states.

These utility values were chosen since EQ-5D is the preferred measure of HRQL in adults, as set out in the reference case. In addition, the model structure and clinical progression is also based on Rombach et al., 2013 thus the definition of health states is consistent with the corresponding utility values. The utility values used in the cost-consequence model are outlined in Table C10.2.

Table C10.2: Summary of utility values for health states in cost-consequence model

State	Utility value	Lower bound	Upper bound	Health state from Rombach et al., 2013
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

In addition, scenario analysis is conducted utilising alterative data sourced from the systematic literature review (Table C10.3). The alternative values provide estimates of the disutility of events (cardiac, renal or stroke) so scenarios are conducted applying these disutilities to the EQ-5D for patients with asymptomatic Fabry disease from Rombach et al (2013a).

Table C10.3: Summary of utility values for scenario analysis

Health state	Scenario 1: Miners	Scenario 2: Gold	Source
Assumed baseline	0.874	0.874	Rombach et al (2013)
Pain / CEFD	0.762	0.762	Rombach et al (2013)
ESRD	0.774	0.624	Baseline minus disutilities from Miners et al (2002) / Gold et al (2002)
Cardiac complications	0.614	0.674	
Stroke	0.624	0.594	
Multiple complications	0.469	0.259	Assumed to be the sum of half the disutilities applied for each symptom (cardiac, ESRD, stroke)

In addition to health state utilities, utility decrements were also applied to infusions and AEs. Most disutilities for AEs were taken from the Sullivan et al. (2011) utilities catalogue, which provides UK-specific EQ-5D scores for a range of health outcomes. Disutilities for AEs are shown in Table C10.4.

Table C10.4: Summary of adverse event disutilities used in cost-consequence model

Event	Utility value	Lower bound	Upper bound	Source
Headache	-0.078	-0.088	-0.068	Sullivan et al. (2011) (migraine)
Influenza	-0.162	-0.194	-0.130	Derived from total QALY loss of 0.00222 (CRD/CHE Technology Assessment Group, 2008; Turner et al., 2003)
Dyspnoea	-0.090	-0.116	-0.064	Sullivan et al. (2011) (other respiratory)
Upper respiratory tract infection	-0.018	-0.027	-0.010	Sullivan et al. (2011) (chronic sinusitis)
Urinary tract infection	-0.053	-0.069	-0.037	Sullivan et al. (2011) (urinary tract disorder)
Gastritis	-0.130	-0.161	-0.099	Sullivan et al. (2011) (gastritis and duodenitis)

Durations for AEs are largely based on the assumption that these events are mild and short lived. Durations applied in the model are shown in Table C10.5. The total annual utility decrement per year is calculated as the annual probability of a patient having each adverse event, multiplied the expected duration of the event (in years), multiplied by the utility for each AE.

Table C10.5: Duration of adverse events

Adverse event	Days per year	Lower bound	Upper bound	Source
Headache	1	0.5	2	Assumption
Influenza	5	3	7	Assumption based on duration of symptoms in clinical trials: (CRD/CHE Technology Assessment Group, 2008; Turner et al., 2003)
Dyspnoea	3	1	5	Parshall et al (2001)
Upper respiratory tract infection	3	1	5	Assumption
Urinary tract infection	2	1	3	Assumption
Gastritis	3	1	5	Assumption

Given the significant difference in administration of migalastat to existing treatment (ERT), a discrete choice experiment (DCE) was conducted to explore the value of moving to an oral therapy and the gain in quality of life from the avoidance of infusion reactions (Lloyd et al., 2016). DCEs can provide valuable information about the relative importance of different treatment attributes, and show how much each attribute may influence treatment decision-making. The aim of the DCE was to evaluate the relative importance of treatment characteristics of Fabry's disease to the respondents and to establish their willingness to trade attributes against each other. In this study the general public were recruited in order to get insight into the value that the public place on treatment innovation in a rare disease. The attributes evaluated in this study included:

(1) Life expectancy (in years)

(2) Mode of administration of treatment

(3) Frequency of reaction to the treatment

(4) Frequency of headache as a side effect

(5) Long-term risk of developing antibodies.

Survey participants were recruited through a specialist recruitment panel in the UK. A sample of 506 people that approximately reflect the UK population demographics in terms of gender, age, ethnicity and geographic distribution participated in the study.

A mixed logit model was used with a transformed survival attribute, which considers the value of an additional year of life with respect to each participants' age and their predicted overall survival (based on their age). This significance and magnitude of the regression coefficients indicate the relative importance of those attributes that statistically influence respondents' choices (Lagarde and Blaauw, 2009).

In this analysis, all of the attributes were statistically significant predictors of choice and therefore the respondents considered each of the attributes when they were making their decisions. Participants expressed a strong preference for a tablet every other day compared to the infusion treatment bi-weekly. Participants also preferred to avoid treatments with headaches and treatments with some form of treatment reaction (such as flu like symptoms). Participants were perhaps least concerned about the risk of antibody formation which is likely due to not fully appreciating the clinical implications of antibodies.

The ratio of any two coefficients was used to estimate the marginal rate of substitution (MRS), which represents the trade-offs made between the two attributes. The results indicate how much participants prefer tablets to bi-weekly infusions. The MRS between this level and overall survival expresses how many years of additional life the respondents would consider equivalent to receiving treatment by infusion for the rest of their life. This is based on the assumption that they have infusions for the rest of their life (and there are no other external influences on HRQL).

The MRS of 1/0.56 = 1.79 for a nurse-administered infusion implies that a participant is willing to trade 1.79 years of life to avoid nurse-administered infusions every year for the rest of their life (and instead receive the tablet). The sample had a mean age of 46.9 years and was 50.8% female. The expected years to live in England for a 46 year old is 35 years for males and 38 years for females years (Office for National Statistics, 2014) thus it was estimated that the sample had 36.6 years of life left. Over a 36.6-year life span, assuming life in full health, this trade-off equates to 1.79/36.6 = 0.049 loss of QALYs per year. Thus, respondents are indifferent between:

i. 36.6 years of life with bi-weekly nurse-administered infusions per year, and

ii. 34.8 years of life in full health (i.e. 34.6 years - 1.79).

Applying this rationale, disutilities for differences in attribute levels were estimated (Table C10.6).

Table C10.6: Results of DCE used to derive infusion disutilities using full study population

Attribute	Coefficient (mean, SD)	MRS of increase in remaining life expectancy by one year	Years willing to trade to avoid infusion	Disutility
Remaining life expectancy in years (continuous variable)				
Increase in remaining life expectancy by one year	0.454 (0.531)	-	-	-
Mode of administration (reference category: tablet)				
Nurse-administered infusion	-0.816 (0.088)	0.56 (0.48; 0.63) [=0.454/0.816]	1.79 (1.59; 2.08)	0.049 (0.043; 0.057)
Self-administered infusion	-0.853 (0.745)	0.53 (0.45; 0.61) [=0.454/0.853]	1.89 (1.64; 2.22)	0.052 (0.044; 0.061)
Reaction to the treatment (reference category: never experience a reaction to your treatment)				
Reaction to your treatment about 6 times a year	-0.318 (0.006)	1.43 (1.02; 1.83)	0.70 (0.55; 0.98)	0.019 (0.015; 0.027)
Reaction to your treatment about 12 times a year	-0.567 (0.128)	0.80 (0.66; 0.94)	1.25 (1.06; 1.52)	0.034 (0.029; 0.042)
Side effects: headache (reference category: No headaches from treatment)				
Headaches 6 times a year treatable with painkillers	-0.448 (0.018)	1.01 (0.80; 1.22)	0.99 (0.82; 1.25)	0.027 (0.022; 0.034)

Headaches 12 times a year treatable with painkillers	-0.742 (0.429)	0.61 (0.52; 0.70)	1.64 (1.43; 1.92)	0.045 (0.039; 0.052)
Long term use of treatment (reference category: no known risk of developing antibodies)				
15% or under 1 in 7 people will develop antibodies in a few years	-0.149 (0.019)	3.05 (1.35; 4.76)	0.33 (0.21; 0.74)	0.009 (0.006; 0.020)
25% or under 1 in 4 people will develop antibodies in a few years	-0.437 (1.134)	1.04 (0.74; 1.34)	0.96 (0.75; 1.35)	0.026 (0.020; 0.037)

Response checks showed that 53 respondents failed the dominant choice test (just over 10%). Excluding the responses of these 53 patients leads to more robust but comparable mean results with reduced uncertainty (Table C10.7). This analysis based on 453 participants was therefore used in the base case analysis.

Table C10.7: Results of DCE used to derive infusion disutilities excluding 53 patients that failed the consistency check

Attribute	Coefficient (mean, SD)	MRS of increase in remaining life expectancy by one year	Years willing to trade to avoid infusion	Disutility
Remaining life expectancy in years (continuous variable)				
Increase in remaining life expectancy by one year	0.549 (0.027)	-	-	-
Mode of administration (reference category: tablet)				
Nurse-administered infusion	-0.995 (0.051)	0.55 (0.48; 0.62)	1.81 (2.07; 1.61)	0.050 (0.057; 0.044)
Self-administered infusion	-1.062 (0.063)	0.52 (0.44; 0.59)	1.93 (2.25; 1.70)	0.053 (0.061; 0.046)
Reaction to the treatment (reference category: never experience a reaction to your treatment)				
Reaction to your treatment about 6 times a year	-0.353 (0.048)	1.56 (1.12; 1.99)	0.64 (0.89; 0.50)	0.018 (0.024; 0.014)
Reaction to your treatment about 12 times a year	-0.648 (0.050)	0.85 (0.70; 0.99)	1.18 (1.42; 1.01)	0.032 (0.039; 0.028)
Side effects: headache (reference category: No headaches from treatment)				
Headaches 6 times a year treatable with painkillers	-0.604 (0.050)	0.91 (0.75; 1.07)	1.10 (1.34; 0.93)	0.030 (0.037; 0.026)
Headaches 12 times a year treatable with painkillers	-0.918 (0.053)	0.60 (0.52; 0.68)	1.67 (1.93; 1.48)	0.046 (0.053; 0.040)
Long term use of treatment (reference category: no known risk of developing antibodies)				

15% or under 1 in 7 people will develop antibodies in a few years	-0.280 (0.047)	1.96 (1.29; 2.63)	0.51 (0.78; 0.38)	0.014 (0.021; 0.010)
25% or under 1 in 4 people will develop antibodies in a few years	-0.686 (0.064)	0.80 (0.64; 0.96)	1.25 (1.56; 1.04)	0.034 (0.043; 0.028)

To be conservative, only disutilities relating to the mode of administration was used in the base case analysis. A worst case scenario in which patients receiving migalastat had 12 headaches per year and patients receiving ERT had 12 reactions to treatment per year, headaches 12 times per year and 25% developed antibodies was explored in sensitivity analysis. In this scenario, the disutilities for each attribute are added together to give an ERT disutility per year of 0.164 with ERT and 0.040 with migalastat.

According to clinical expert opinion, it is assumed that 50% of patients require a nurse to deliver infusions, while the remaining 50% of patients self-administer infusions or have infusions administered by an informal caregiver. The DCE-derived disutilities relating to infusion administration are therefore included in the model using a 50% weighting, equating to an overall annual disutility due to infusions of 0.052 (95% CI 0.045 - 0.059), which is applied to all ERT patients receiving treatment for the duration of the model.

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The disutility applied for infusions was ratified by a clinical expert. Clinical experts did not validate or estimate any other HRQL values.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

A patient's HRQL is initially 0.762 if starting in the pain or CEFD state. Once a patient has transitioned from CEFD into one of the complications states (ESRD, cardiac or stroke), HRQL is slightly reduced again, by 0.018. If a patient develops another complication and enters a double complication state, their HRQL will drop most to the lowest health state utility (0.584). From a double complication, a patient's HRQL is not considered to decrease again if they develop a third complication and transition to that state. The HRQL is assumed constant in individual health states.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Data in the literature demonstrates that there are many symptoms of Fabry disease that affect patients' quality of life that are not explicitly captured in the model due to lack of data on transition probabilities between health states. For example, gastrointestinal manifestations of Fabry disease often have profound negative effects on quality of life (Gold et al., 2002). Depression has also been shown to seriously impact quality of life in patients with Fabry disease (Miners et al., 2002; Gold et al., 2002; Street et al., 2006).

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL changes with transitions between some states and at the occurrence of adverse events, but it is otherwise assumed constant over time within health states.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

The utility estimates for health states and adverse events taken from the literature have not been amended.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No treatment continuation rule has been assumed. Clinical experts have stated that they will follow the existing English guidelines for ERT (Table B8.2) when treating patients with migalastat, following the starting and stopping criteria as in the national guidelines (Hughes et al., 2013a). These guidelines do not include any treatment continuation rules.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

Please see Appendix 17.1.

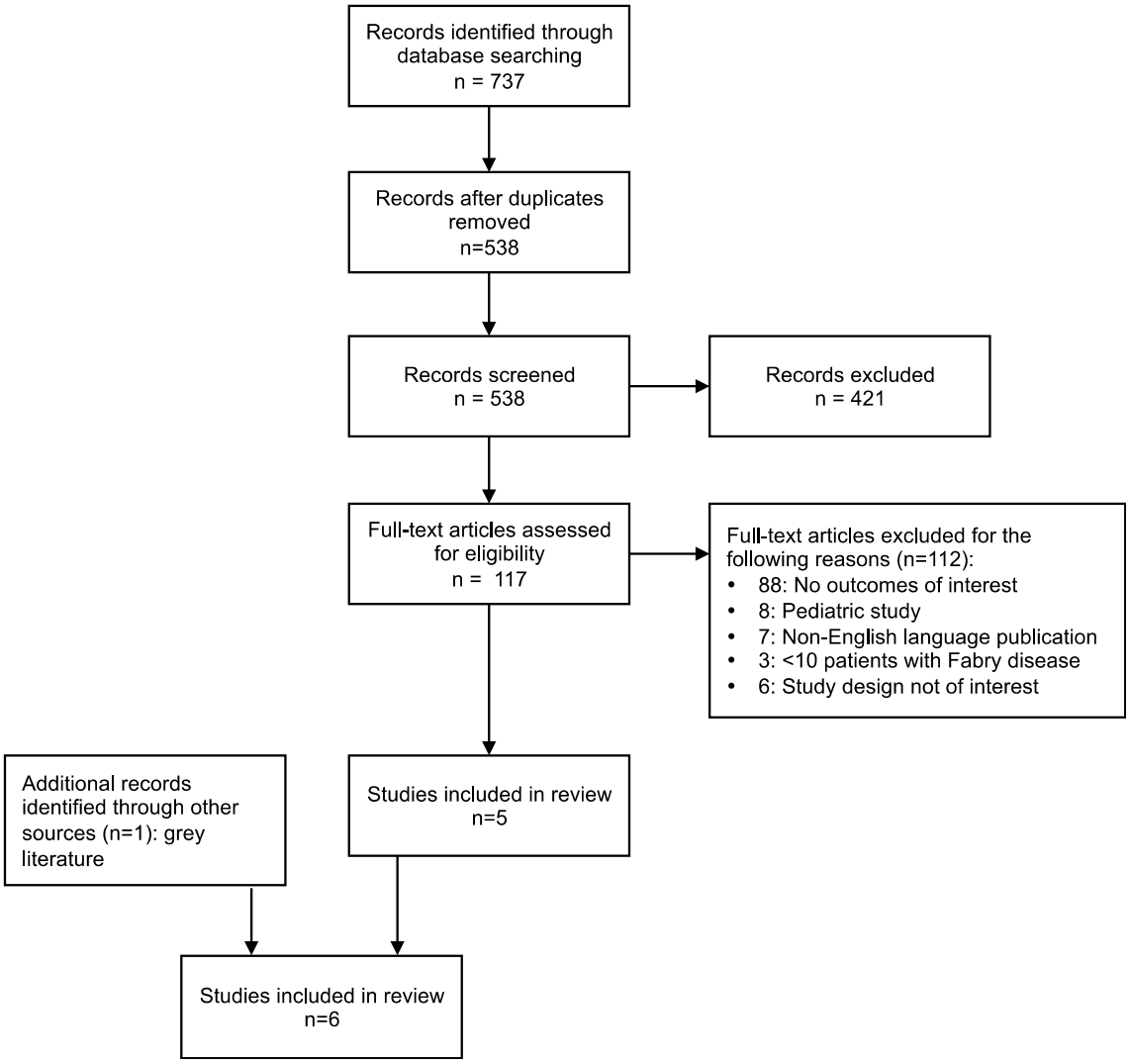
11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

Please see Appendix 17.1.6.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The numbers of published studies included and excluded at each stage are illustrated in a PRISMA diagram, presented as Figure D11.1.

Figure D11.1: PRISMA diagram for economic systematic review



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope.

Table D11.1: Summary list of all evaluations involving costs

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
Connock et al. (2006)	UK	Comparators: untreated patients with Fabry disease and those treated with ERT. Untreated patients were assigned independent lifetime risks of developing each of the following clinical symptoms: renal insufficiency, cardiac symptoms, cerebrovascular symptoms, neuropathic pain, angiokeratoma, hypertension and hyperlipidaemia. Patients treated with ERT were assumed to have no Fabry's disease-specific mortality.	The model considered a birth cohort of male patients with Fabry disease that were followed up until death.	Monitoring costs were assumed to be the same for the treated and untreated cohorts and therefore the model excludes these costs. Costs were expressed in 2003-4 prices, £: • Renal dialysis 23,504 • Graft transplant 10,249 • Graft rejection 23,681 • Functioning graft 886 • LVH 20 • Mechanical ventilation 1,928 • Disabling stroke 14,150 • Mild stroke 1,364 • Neuropathic pain 78 • Hypertension 40 • Hyperlipidaemia 235	It was assumed that patients regain full health immediately upon treatment and become ill immediately were it to be stopped. Utilities were dependent only on treatment rather than disease state (0.6 for untreated patients and 0.94 [age-dependent] for treated patients).	<u>Base case</u> • Cost no treatment £34,330 • Cost ERT £2,572,122 • Incremental cost £2,537,792 • QALYs no treatment 14.69 • QALYs ERT 24.76 • Incremental QALYs 10.07 • ICER £252,112 <u>Sensitivity analysis</u> • ERT does not restore full health (treated patients to gain a utility increment of 0.10 from treatment) ICER £602,831 • Life expectancy of untreated cohort set to 50 years rather than 54.8 years ICER £241,063

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
Guest et al. (2011)	Italy	A budget impact analysis estimating the resource implications of managing adults with Fabry disease with agalsidase alfa, agalsidase beta or no ERT, from the perspective of the Italian national healthcare system. A decision model was constructed in TreeAge Pro 2009 with the following health states: 1) patients received either no treatment, agalsidase alfa or agalsidase beta; 2) followed by hospital infusions for those on treatment (treatment at home was explored in a sensitivity analysis).	Newly diagnosed adults (≥ 18 years at time of presentation) with Fabry disease following referral to a specialist in Italy	Annual resource costs were reported in 2008/09 prices. Costs considered included clinician visits, test/procedures, ERT, day ward attendances, comedication and dialysis. It was assumed that the cost of medication for agalsidase alfa would be the same as that of agalsidase beta. It was also assumed that patients treated with agalsidase alfa would be in the day ward for 2 hours vs. 5 hours for those on agalsidase beta.	N/A – evaluation was a budget impact analysis only Agalsidase alfa and agalsidase beta were assumed to have similar clinical effectiveness profiles.	**Expected total annual cost per patient**: <u>First year following diagnosis</u>: Agalsidase alfa: €115,384.00 Agalsidase beta: €116,432.00 No ERT: €2,836.00 <u>After first year:</u> Agalsidase alfa: €164,121.00 Agalsidase beta: €165,635.00 No ERT: €639.00 ERT was the principal cost driver, accounting for > 95% of the expected costs. Diagnostic tests and procedures that are undertaken on an annual basis were the principal cost drivers among patients not on ERT.
Guest et al. (2010)	Two specialised centres for Fabry disease in Norway	A budget impact analysis estimating the resource implications of managing adults with Fabry disease with agalsidase alfa, agalsidase beta or no ERT, from the perspective of the publically funded healthcare system in	Newly diagnosed adults, ≥ 18 years of age at the time of presentation with Fabry disease in Norway	Annual resource costs were reported in 2008/09 prices. Costs were obtained from the Oslo and Bergen Fabry centres and included hospital admission, clinician visits, day ward	N/A – evaluation was a budget impact analysis. Agalsidase alfa and	The expected annual cost of managing patients with Fabry disease represents 0.05% of the current annual healthcare budget in Norway. ERT accounted for 89% of these costs. **Expected total annual cost per patient**: <u>First year following diagnosis</u>:

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
		Norway. As per Guest et al (2011), a decision model was constructed in TreeAge Pro 2007 with the following health states: 1) no treatment, 2) agalsidase alfa followed by hospital infusions, or 3) agalsidase beta followed by hospital infusions.	following referral to a specialist	attendance, and various tests/procedures costs.	agalsidase beta were assumed to have similar clinical effectiveness profiles.	Agalsidase alfa: NOK 927,707.35 Agalsidase beta: NOK 975,008.40 No ERT: NOK 158,691.00 After first year: Agalsidase alfa: NOK 1,556,559.62 Agalsidase beta: NOK 1,639,979.50 No ERT: NOK 80,910.00
Moore et al. (2007)	US	A cost-effectiveness analysis comparing ERT with standard medical care from a third-party payer perspective. Incremental cost per QALY and INB ratio distributions were obtained by bootstrapping of normal distributions (n=1,000) with the following properties included: 1) baseline utility = 0.56 (SD 0.35); and (2) utility following 1 year of treatment = 0.75 (SD 0.35).	Fabry disease, no other characteristics presented	The only cost details provided were estimated standard medical care and ERT yearly costs. Estimated costs of standard medical care for Fabry-Anderson disease per year: $US 25,000 (SD 5,000) Estimated yearly acquisition cost of ERT: $US 250,000 (SD 35,000). Cost year NR	Utility (specific values not reported) Estimates of the mean baseline $EQ_{utility}$ and SD were taken from Miners et al. 2002. Estimates of the effect of ERT were determined from Beck et al. 2004, which involved 545 patients from the Fabry	Assumption—probability of INB > 0 There was an 80% probability that ERT had a positive net benefit at a cost per QALY of around $300,000. Assumption—using a sceptical Bayesian prior with <5%chance of a net benefit and assuming a Normal likelihood distribution, the posterior distribution Mean ICER ≈$175,000 Assumption—using an enthusiastic Bayesian prior with >95% chance of a net benefit and assuming a Normal likelihood distribution, the posterior distribution) Mean ICER ≈$350, 000. Authors noted that 1) ERT was not

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
					Outcome Survey	cost-effective given current market pricing and current effectiveness evidence; and 2) WTP for treatment was influenced by different assumptions about treatment response.
Rombach et al. (2013a)	The Netherlands	A Markov state-transition, cost-effectiveness analysis comparing ERT with standard medical care from a societal perspective over a lifetime horizon (70 years). The model had 11 disease states. It was assumed that patients could die in all states. The cycle length for the model was one year. Data on disease progression prior to and following the introduction of ERT were gathered from medical chart reviews. Key assumptions made due to data availability: 1) State transition probabilities for the natural (untreated) course of Fabry disease were based on the	Fabry disease patients based on data from the Dutch Fabry Cohort, which included 116 adults and 26 children (age range: 5–78 years) Among these patients, 75 started ERT on indication.	Costs (2009 Euros) included direct and indirect medical costs of healthcare use, as well as the indirect cost of sick leave. Costs were retrospectively and prospectively gathered from the Dutch Fabry cohort. Healthcare volumes and related costs for treated patients were assumed to be similar for males and females in the same disease stage	Transition probabilities and utilities were retrospectively and prospectively gathered from the Dutch Fabry cohort.	**Years free of end-organ damage (YFEOD)** Standard medical care: 55.0 years ERT: 56.5 years Difference: 1.5 years **Undiscounted QALYs** Standard medical care: 48.6 ERT: 50.2 Difference: 1.6 QALYs **Undiscounted ICER**: All: Incremental cost per extra YFEOD: €6,560,885 ICER: €6,065,529 Males: Incremental cost per extra YFEOD: €5,917,091 ICER: €5,451,797

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
		pre-ERT treatment period; 2) ERT only decreased the probability of disease progression; 3) No distinction was made between agalsidase alfa and beta.				Females: Incremental cost per extra YFEOD: €7,527,013 ICER: €6,955,612
Wyatt et al. (2012)	UK	A cost-of-illness analysis to comprehensively assess the financial burden of Fabry disease on the NHS, social care and other publicly funded care and support services. Cost data were collected from hospital clinical records and also estimated using questionnaires administered to patients or carers. Costs were calculated from the perspective of the NHS over the course of 12 months.	Adult patients with Fabry disease; no other specific patient characteristics were provided.	Costs evaluated included: • Treatment costs • In-hospital services (inpatient stays, outpatient visits, day cases, accident and emergency visits) • Services outside hospital (GP visits, home visits, GP nurse appointments, district nurses, community mental health nurse, other nurse or health visitor, counsellor, other therapist, 'alternative' medicine or therapy, psychologist, psychiatrist, other community-based doctor, occupational	N/A – cost analysis.	**Annual cost for ERT per adult patient** Agalsidase alfa 3.5 mg: £120,840 Agalsidase beta 35 mg and/or 5 mg: £106,394 **Annual care cost components** Hospital services: • Total: £2,300 • Inpatient stays: £1,000 • Outpatient visits: £940 • Day cases: £290 Accident and emergency visits: £21 Services outside hospital: • Total: £1,000 • GP visits (including home visits): £110 • GP nurse appointments: £7 • District nurses: £31 • Other nurse or health visitor: £710 • Counsellor: < £1

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
				therapist, social worker, home help, care attendant, community support worker, housing worker, all non-hospital NHS and social-care providers)		• Other therapist: £33 • 'Alternative' medicine or therapy: £120 • Psychologist: £7 • Other community-based doctor: £1 • Occupational therapist: £2 • Social worker: < £1 • Home help: £8 • Housing worker: < £1 • All non-hospital NHS and social care providers: £1,000

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Table D11.2: Quality assessment of health economic studies

Connock et al. (2006)		
Study design		
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	The stated objective of the economic analysis was to estimate the cost-effectiveness of ERT in the management of Fabry's disease compared with standard supportive care.
2. Was the economic importance of the research question stated?	Yes	No published evidence reporting an economic evaluation of ERT for Fabry disease had been identified.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	It was not explicitly stated but the perspective was that of the NHS.
4. Was a rationale reported for the choice of the alternative interventions compared?	N/A	ERT is compared with standard supportive care. ERT (agalsidase alfa and agalsidase beta) is the only licensed treatment for patients with Fabry disease in the UK.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	The stated analysis was cost-effectiveness, but more specifically, it is a cost-utility analysis.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	With limited data available, patients were assumed to regain full health upon treatment with ERT and become ill were it to be stopped. Untreated patients' disease progression was derived from various published sources of time to progression to specific events (e.g. cardiac, renal).
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Multiple published studies were used to derive the transition probabilities for untreated patients.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	No meta-analysis was conducted.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost-effectiveness measured in terms of cost per QALY.

12. Were the methods used to value health states and other benefits stated?	Yes	The HRQL of untreated patients was assumed ot be equivalent to the normal population. The HRQL of patients receiving ERT was estimated as the midpoint of two published studies.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	The HRQL of patients receiving ERT was derived from the literature. The authors conducted a comprehensive systematic review of HRQL in the literature prior to the cost-effectiveness evaluation and therefore full study details are extracted.
14. Were productivity changes (if included) reported separately?	N/A	Productivity losses were not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Productivity losses were not included
16. Were quantities of resources reported separately from their unit cost?	No	Costs were only presented as annual costs.
17. Were the methods for the estimation of quantities and unit costs described?	No	All costs were obtained form the literature.
18. Were currency and price data recorded?	Yes	Costs were expressed in pounds (£) in 2003-04 prices.
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	Details of a specific model structure were not stated. It is stated that in the model, patients were assigned an independent lifetime risk of developing each of the following clinical symptoms: renal insufficiency, cardiac symptoms, cerebrovascular symptoms, neuropathic pain, angiokeratoma, hypertension and hyperlipidaemia.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	In the absence of access to unpublished registry data to inform an understanding of the contribution of the various clinical manifestations to HRQL, several assumptions were made to simplify the decision model. Given the objective of the analyses was to provide a clearer understanding of the likely costs associated with treating Fabry's disease over a patient's lifetime, the model explicitly considered the resource impact from all major cost-incurring events associated with Fabry's disease. The lifetime risk of developing and costs associated with renal insufficiency, cardiac events and cerebrovascular symptoms were explicitly modelled. All other Fabry's disease symptoms were modelled implicitly.

22. Was the time horizon of cost and benefits stated?	Yes	Lifetime from birth
23. Was the discount rate stated?	Yes	3.5%
24. Was the choice of rate justified?	No	No, but it consistent with the UK discount rate as used by NICE.
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	A PSA was deemed not sensible owing to data limitations and the lack of understanding concerning the correlation between the clinical symptoms of the disease
27. Was the approach to sensitivity analysis described?	Yes	A PSA was deemed not sensible owing to data limitations and the lack of understanding concerning the correlation between the clinical symptoms of the disease. Three scenarios were conducted: (1) ERT was not assumed to restore people to full health, (2) life expectancy of the untreated cohort was reduced from 54 to 50 years, and (3) cost of ERT varied.
28. Was the choice of variables for sensitivity analysis justified?	No	Very limited sensitivity analysis was conducted. No sensitivity analysis was conducted on the risk of events or their associated costs, or discount rates.
29. Were the ranges over which the parameters were varied stated?	Partly	In the first scenario, a utility increment of 0.1 was applied to treated patients. This was based on data from Hoffman et al (2005), which is a simplification of the likely lifetime benefits of ERT. The second and third scenarios appear to be arbitrary variations of parameters to test sensitivity.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Incremental costs and incremental QALYs were presented along with the ratio.
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	The estimated cost per QALY gained from ERT treatment was £252,000.
34. Did conclusions follow from the data reported?	No	There was no conclusion as to whether the result meant that ERT could be cost-effective or not.
35. Were conclusions accompanied by the appropriate	Yes	The authors conclude that the results must be considered in the light of the many

caveats?		assumptions used in the model is highlighted. The usefulness of observational data from the Fabry Outcome Survey database (not available at the time) to inform the model is also stated.
36. Were generalisability issues addressed?	No	
Guest et al. (2011)		
Study design	**Budget Impact Model and Cost Analysis**	
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	The research question sought to determine the resource implications and budget impact of managing adults with Fabry disease in Italy.
2. Was the economic importance of the research question stated?	Yes	In Italy, many orphan drugs can only be prescribed by hospital-based specialists. Although Italy has a DRG-based reimbursement system in place, this does not cover the cost of orphan drugs, which are paid for separately from the SSN's central health funds.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The perspective is of the SSN.
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	Agalsidase alfa and beta are the only currently approved treatments for Fabry disease. The gaps in the published evidence base on healthcare resource use pertaining to managing adults with Fabry disease in Italy were estimated by the clinical authors, as well as a nephrologist and cardiologist who were based at six Fabry centres across Italy. This was supplemented with information about patient numbers and patients' prescribed medications obtained from the Italian FOS database, which is an international, physician-driven registry for patients with Fabry disease who are either being treated with agalsidase alfa or not receiving ERT.
5. Were the alternatives being compared clearly described?	Yes	Agalsidase alfa (0.2 mg/kg) Agalsidase beta (1.0 mg/kg)
6. Was the form of economic evaluation stated?	Yes	1. Expected annual cost (Euros at 2008/09 prices) per patient 2. Budget impact (Euros at 2008/09 prices) attributable to managing 220 existing Fabry patients and 20 new patients in Italy each year
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	A cost analysis and budget impact model were developed.

8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	Health states were: treatment with agalsidase alfa (0.2 mg/kg) or agalsidase beta (1.0 mg/kg), or no treatment; clinical effectiveness of the ERT treatments was assumed to be equal. Analysis was of costs associated with each state. Mean unit resource costs at 2008/09 prices obtained from four of the centres were applied to the resource utilization estimates within the model to estimate the annual cost to the public healthcare system of managing these patients in an average year.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	220 patients with Fabry disease in Italy, 32% of whom were treated with agalsidase alfa (0.2 mg/kg), 41% with agalsidase beta (1.0 mg/kg) and 27% with no ERT Additionally, it was estimated that there are 20 new patients per annum, of whom 40% are treated with agalsidase alfa (0.2 mg/kg), 40% with agalsidase beta (1.0 mg/kg) and 20% do not receive any ERT.
14. Were productivity changes (if included) reported separately?	N/A	Analysis did not include productivity lost
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	There is a description of the percentage of patients using resources in Table 1, and separate unit costs are reported in Table 2.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	Estimates are reported in 2008/09 Euros
19. Were details of price adjustments for inflation or currency conversion given?	N/A	

20. Were details of any model used given?	Yes	A decision model was constructed in TreeAge Pro 2009.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
22. Was the time horizon of cost and benefits stated?	Yes	Annual estimates
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	Deterministic sensitivity analyses were performed to assess whether healthcare resources could be used more efficiently by potentially switching patients from agalsidase beta to agalsidase alfa and vice versa.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	The costs of treatment with agalsidase alfa and agalsidase beta were comparable. Since agalsidase alfa is the only ERT for Fabry disease that has been licensed for home treatment in Italy, its use has the potential to reduce healthcare costs and release hospital resources in different specialties for alternative use by non-Fabry patients, thereby improving the efficiency of the public healthcare system in Italy compared to agalsidase beta.

35. Were conclusions accompanied by the appropriate caveats?	Yes	This is answered in the response for the next question.
36. Were generalisability issues addressed?	Yes	Results may be confounded by certain limitations within the model. The model only considered resource use and corresponding costs for an 'average patient' and did not take into account such factors as comorbidities, disease severity, suitability of patients for different treatments and other disease-related factors. The resource use estimates in the model were derived retrospectively rather than prospectively measured. Consequently, treatment patterns and associated healthcare resource use for the 'average Fabry patient' throughout Italy may not be the same as for those patients who were managed by the study's clinical authors.
Guest et al. (2010)		
Study design	**Budget Impact Model and Cost Analysis**	
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	The research question sought to determine the resource implications and budget impact of managing adults with Fabry disease in Norway.
2. Was the economic importance of the research question stated?	Yes	In Norway, the cost of ERT is mostly funded by the NAV. The NAV only funds ERT when infused in the community and not in a hospital; if the patient receives the treatment in a hospital, the institution pays for the enzyme with existing funds. Consequently, there is a drive for Fabry patients to receive their ERT in the community as quickly as possible.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The perspective is of the publicly funded Norwegian healthcare system.
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	Agalsidase alfa and beta are the only currently approved treatments for Fabry disease. The gaps in the published evidence base on healthcare resource use pertaining to managing adults with Fabry disease in Norway were estimated by the clinical authors who are based at the two Fabry centres in Norway and who collectively manage approximately 60 adults with Fabry disease.
5. Were the alternatives being compared clearly described?	Yes	Agalsidase alfa (0.2 mg/kg) Agalsidase beta (1.0 mg/kg)
6. Was the form of economic evaluation stated?	Yes	1. Expected annual cost (NOK at 2008/09 prices) per patient

		2. Budget impact (NOK at 2008/09 prices) attributable to managing 60 existing Fabry patients and 4 new patients in Norway each year
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	A cost analysis and budget impact model were developed.
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	Health states were: treatment with agalsidase alfa (0.2 mg/kg) or agalsidase beta (1.0 mg/kg), or no treatment; clinical effectiveness of the ERT treatments was assumed to be equal. Analysis was of costs associated with each state. Mean unit resource costs at 2008/09 prices obtained from the two specialised centres were applied to the resource utilisation estimates within the model to estimate the annual cost to the public healthcare system of managing these patients in an average year.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	60 patients with Fabry disease in Norway, 23% of whom were treated with agalsidase alfa (0.2 mg/kg), 30% with agalsidase beta (1.0 mg/kg) and 47% with no ERT Additionally, it was estimated that there are 4 new patients per annum, of whom 23% would be treated with agalsidase alfa (0.2 mg/kg), 30% with agalsidase beta (1.0 mg/kg) and 47% do not receive any ERT.
14. Were productivity changes (if included) reported separately?	N/A	Analysis did not include productivity lost
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	There is a description of the percentage of patients using resources in Table 1, and separate unit costs are reported in Table 2.

17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	Estimates are reported in 2008/09 NOK
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	A decision model was constructed in TreeAge Pro 2007.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
22. Was the time horizon of cost and benefits stated?	Yes	Annual estimates
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	Deterministic sensitivity analyses were performed to assess whether healthcare resources could be used more efficiently by potentially switching patients from agalsidase beta to agalsidase alfa and vice versa.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Based on clinical practice at Norway's two reference centres for Fabry disease,

		maximizing the proportion of patients undergoing home-based infusions had the potential to release community-based resources for alternative use by non-Fabry patients, thereby improving the efficiency of the publicly funded healthcare system. Future analysis of QOL and indirect societal costs would be helpful in gaining a better understanding of the socioeconomic impact of this disease.
35. Were conclusions accompanied by the appropriate caveats?	Yes	This is answered in the response to the next question.
36. Were generalisability issues addressed?	Yes	Results may be confounded by certain limitations within the model. The model only considered resource use and corresponding costs for an 'average patient' and did not take into account such factors as comorbidities, disease severity, suitability of patients for different treatments and other disease-related factors. The resource use estimates in the model were derived retrospectively rather than prospectively measured. Consequently, treatment patterns and associated healthcare resource use for the 'average Fabry patient' may not be the same for all patients who are managed by study's clinical authors.
Moore et al. (2007)		
Study design	**Cost-effectiveness analysis**	
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	Determine upper and lower bounds around current pricing structure of ERT using a range of probabilities for incremental net benefit of treatment
2. Was the economic importance of the research question stated?	Yes	Decision makers and health administrations may be able to reach more guided appropriation decisions after consideration of funding models relevant to orphan and ultra-orphan drug therapy; this would contribute to the discussion of alternative funding models in relation to lysosomal storage diseases, and in particular Fabry-Anderson disease.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The perspective is that of a US third-party payer.
4. Was a rationale reported for the choice of the alternative interventions compared?	N/A	
5. Were the alternatives being compared clearly described?	N/A	
6. Was the form of economic	Yes	A cost-effectiveness acceptability curve

evaluation stated?		was developed relating the willingness to pay to the probability that the incremental net benefit of treatment was >0.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Bootstrap estimates of the incremental net benefit statistics were developed. This statistical technique is particularly useful when limited data are available, as is the case with utility studies of ERT in Fabry-Anderson disease. These bootstrap estimates were combined with the cost-effectiveness acceptability curve and were further developed with a Bayesian analysis of 'best-case' and 'worst-case' scenarios for the incremental net benefit of ERT treatment.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Estimates of the effect of ERT were determined from Beck et al. 2004,[5] a study involving 545 patients from the FOS.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Based on one study referenced in previous question
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	All publications used for the analysis are referenced in this publication; no meta-analyses were performed.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Incremental cost per QALY distribution INB metric distribution
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	This study does not report information for productivity lost.
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	N/A	
17. Were the methods for the estimation of quantities and unit costs described?	N/A	
18. Were currency and price data recorded?	Yes	Outcomes reported in USD
19. Were details of price adjustments for inflation or currency conversion given?	N/A	

20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	N/A	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Upper and lower bound for market pricing based on the current market cost of ERT in Fabry disease are reported
27. Was the approach to sensitivity analysis described?	No	Sensitivity analysis NR
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	Yes	Incremental cost per QALY distribution
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	The cost of ERT will always result in a net deficit to society under current costing and ERT efficacy as determined by the QALY metric. The rules of fair cooperation should govern decision making for ERT in Fabry-Anderson disease and for funding therapeutic advances in other rare diseases belonging to the orphan and ultra-orphan categories.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations included the paucity of Fabry-Anderson disease-related economic assessment investigations and the use of the QALY metric for utility.
36. Were generalisability issues addressed?	No	

Rombach et al. (2013a)		
Study design	**Cost-effectiveness analysis**	
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	To evaluate the costs and effects of ERT against standard medical care
2. Was the economic importance of the research question stated?	Yes	Due to the increasing number of orphan drugs and their extremely high costs, there is a need for more transparent pricing and reimbursement of orphan drugs, including cost-effectiveness analyses.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Perspective of the analysis is the Dutch healthcare system
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	Agalsidase alfa and agalsidase beta were treated as equivalent in this study; they were together considered as ERT as evidence of superiority for either product is lacking and they are of comparable cost.
5. Were the alternatives being compared clearly described?	Yes	The comparison in this analysis was between ERT and no ERT (standard medical care).
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis Cost data included the direct and indirect medical costs of healthcare use as well as the indirect non-medical costs of sick leave.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	A life-time Markov state-transition model of the course of Fabry disease evaluated the costs and effects of ERT against standard medical care.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Data on disease progression prior to and following the introduction of ERT were gathered from medical chart reviews.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Data used to estimate the probability of transition to the next health state, utilities and costs were retrospectively and prospectively gathered from the Dutch Fabry cohort including 116 adults and 26 children. Among these patients, 75 started ERT on indication.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	The incremental lifetime effects of ERT, incremental lifetime costs of ERT, and ICERs were the main outcomes of interest.
12. Were the methods used to value health states and other benefits stated?	Yes	Health status profiles were gathered quarterly with the EQ-5D quality of life questionnaire; then associated, time trade-

		off based health utilities were averaged per patient per disease state and subsequently, per disease state over patients. The model was composed of 11 disease states, including death.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Data based on Dutch Fabry cohort including 116 adults and 26 children
14. Were productivity changes (if included) reported separately?	Yes	Indirect costs of production loss are separately added in Table 6 – scenario-analyses
15. Was the relevance of productivity changes to the study question discussed?	Yes	Adding the indirect costs of productivity loss to the total medical costs marginally affects the ICERs.
16. Were quantities of resources reported separately from their unit cost?	No	The resource use data from the AMC in Amsterdam were linked to available real unit costs from the AMC hospital ledger, detailed in Table 2. Unit costs were price indexed for the year 2009 (Euros). However, the quantities of resources used are not reported.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	As stated above, resource used was derived from the patients via quarterly disseminated questionnaires and linked to the appropriate unit costs in Euros from the most recent Dutch costing manual.
18. Were currency and price data recorded?	Yes	Cost information is given in 2009 Euros.
19. Were details of price adjustments for inflation or currency conversion given?	N/A	There was no inflation or conversion used.
20. Were details of any model used given?	Yes	It is a lifetime Markov state-transition model of the course of Fabry disease. The 11 health states are described above.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	This model was selected to include the longer-term consequences of treatment.
22. Was the time horizon of cost and benefits stated?	Yes	The model was run from a lifetime perspective, starting asymptomatically at birth until the age of 70 years or death. Hypothetical cohorts of treated and untreated male and female patients were compared for both primary outcomes: costs per year without end-organ damage and costs per QALY.
23. Was the discount rate stated?	Yes	Discount rate was 1.5% for effects and 4% for costs
24. Was the choice of rate justified?	Yes	Univariate sensitivity analyses have been restricted to the choice of discount rate to account for time preference (discounting of effects by 1.5% and costs by 4% instead of no discounting).

25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Not clear	Statistical methods are not reported separately, but CIs are included in reported outcomes.
27. Was the approach to sensitivity analysis described?	Yes	Sensitivity analyses are reported in the publication: differential discounting effects (1.5% vs. 4%); 25% reduction of the yearly cost of ERT The sensitivity and scenario analyses revealed that cost-effectiveness ratios could be substantially reduced by lowering the high costs of the drug itself (near proportional impact) or a modest health gain of 0.1 QALY per year in treated patients (minus 80%).
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Table 5 includes the discounted and undiscounted incremental lifetime cost-effectiveness ratios, overall and by gender. ICER based on YFEOD: €6.6 million (€5.9 million for males and €7.5 million for females); the incremental costs per QALY gained: €6.1 million (€5.5 million for males, €7.0 million for females).
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	The model demonstrated small gains in effectiveness with 1.5 extra YFEOD and 1.6 QALYs gained (or both 0.7, discounted) for treatment with ERT.
34. Did conclusions follow from the data reported?	Yes	The conclusion in this study showed that the affordability of ERT for Fabry disease remains at stake. The modest effectiveness drives the costs per QALY and even the costs per YFEOD to numbers expressed in millions of Euros. This study recommends that new therapeutic guidelines should be developed to differentiate high responders from low or no responders to ERT, diagnostic procedures should be improved, and the add-on value of ERT relative to the effect of ACE-ARB should be assessed.

35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations are presented in the discussion paragraph: exclusion of costs of follow-up related to a kidney transplant in particular; only the costs of a kidney transplant during its first year were incorporated. Including these follow-up costs would have increased the structural complexity of the memory-less Markov model considerably without – in view of the small number of Dutch Fabry patients receiving a kidney transplant – meaningful consequences in terms of health policy.
36. Were generalisability issues addressed?	Yes	To evaluate the costs and effects of ERT against standard medical care
Wyatt et al. (2012)		
Study design	**Cost-of-illness analysis**	
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	To determine the cost of ERT (agalsidase alfa and beta, costs detailed separately) and cost of care for adult patients with Fabry disease
2. Was the economic importance of the research question stated?	No	To assess comprehensively the financial burden of Fabry disease on the NHS, social care and other publicly funded care and support services
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The perspective is that of the UK NHS.
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	Agalsidase alfa and beta are the only approved treatments for Fabry disease. At recruitment, 212 adults were on ERT with 123 adult patients receiving agalsidase beta, 88 adult patients receiving agalsidase alfa, and one patient's treatment was unknown. Annual NHS costs were reported per patient for both therapies.
5. Were the alternatives being compared clearly described?	Yes	Annual NHS cost per Fabry disease patient for: agalsidase alfa 3.5 mg and agalsidase beta 35 mg and/or 5 mg
6. Was the form of economic evaluation stated?	Yes	Cost-of-illness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Annual NHS cost per adult patient with Fabry disease (2011) in terms of ERT and care costs
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	No. (%) of patients (out of the 257 patients with valid resource use data) who used the following services: hospital services (total services and break down), services outside hospital (total services and break down) and total healthcare (NHS) and social care costs
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Data for unit cost estimates and quantities were provided by the National Specialised Commissioning Team, and for quantities by patient self-report.
18. Were currency and price data recorded?	Yes	Outcomes reported in GBP
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	N/A	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals	Yes	Mean cost, SD, median cost, interquartile range

given for stochastic data?		
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	N/A	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Breakdown of the cost of NHS hospital services and the cost of NHS and social care services outside hospital
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Based on patients' self-reported health- and social-care service use, the annual cost of caring for people with Fabry disease, excluding the purchase cost of ERT, was estimated at £3,300. These costs were dwarfed by the costs of the therapies, the mean annual costs of which ranged from £108,242 to £120,840, depending on the treatment used.
35. Were conclusions accompanied by the appropriate caveats?	N/A	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

12 De novo cost-consequence analysis

Section 12 requires the sponsor to provide information on the de novo cost-consequence analysis.

The de novo cost-consequence analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-consequence analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-consequence analysis?

All patients with Fabry disease that meet the expected licenced indication for migalastat are included in the analysis, that is, patients who have amenable mutations who are at least 16 years' old and do not have ESRD.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-consequence analysis is different from the scope.

In line with the scope, both agalsidase alfa and agalsidase beta are included in the cost-consequence model. However, no head to head studies have shown convincing evidence on clinical grounds for superiority or non-inferiority of either of these treatments (Biegstraaten et al., 2015) and therefore agalsidase alfa and agalsidase beta are are considered to be clinically equivalent (see Section 8.2). In addition, the clinical study compared migalastat compared to a pooled comparator "ERT" and other published sources of data used for the cost-consequence model are for ERT, rather than specifically agalsidase alfa or agalsidase beta. Therefore, in line with the clinical study and published disease progression data, the comparator used in the cost-consequence model is ERT. English clinical experts have estimated that the market shares of ERT are 70% agalsidase alfa and 30% agalsidase beta, thus a weighted average of the cost for ERT treatment and administration has been derived.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

As detailed in section 11, three cost-effectiveness analyses were obtained from the systematic literature review:

1. Connock et al 2006
2. Moore et al 2007
3. Rombach et al 2013

As detailed in Table D11.1, Connock et al (2006) compared untreated patients with Fabry disease to those treated with ERT. Untreated patients were assigned independent lifetime risks of developing each of the following clinical symptoms: renal insufficiency, cardiac symptoms, cerebrovascular symptoms, neuropathic pain, angiokeratoma, hypertension and hyperlipidaemia. To assess the cost-effectiveness of ERT, it was assumed that patients regain full health immediately upon treatment and become ill immediately were it to be stopped. Patients treated with ERT were assumed to have no Fabry's disease-specific mortality. In addition, utilities were dependent only on treatment rather than disease state (0.6 for untreated patients and 0.94 [age-dependent] for treated patients). All these assumptions mean that in essence the model assumed a 'perfect drug scenario', which is not an accurate reflection of the progressive nature of Fabry disease or the treatments available and was therefore not considered to inform the model structure of this evaluation.

Moore et al (2007) conducted a statistical analysis to estimate incremental cost per QALY and incremental net benefit of ERT. Health states were not applied, but rather results were obtained by bootstrapping of baseline utility, utility after a year of treatment, cost of medical care and cost of ERT. This is a simplistic analysis that does simulate progression through disease states and is therefore an inappropriate basis for this analysis.

In contrast, Rombach et al (2013) created a well-designed and reported Markov state-transition, cost-effectiveness analysis comparing ERT with standard medical care from a societal perspective over a lifetime horizon with 11 disease states that captured the key symptoms of Fabry disease. Data for the estimation of transition probabilities, utilities and costs were retrospectively and prospectively gathered from the Dutch Fabry cohort. Data on disease progression prior to and following the introduction of ERT were gathered from medical chart reviews. Consequently, this study provided a robust basis for the evaluation of migalastat compared to ERT, both in terms of the model structure as well as clinical and resource use inputs.

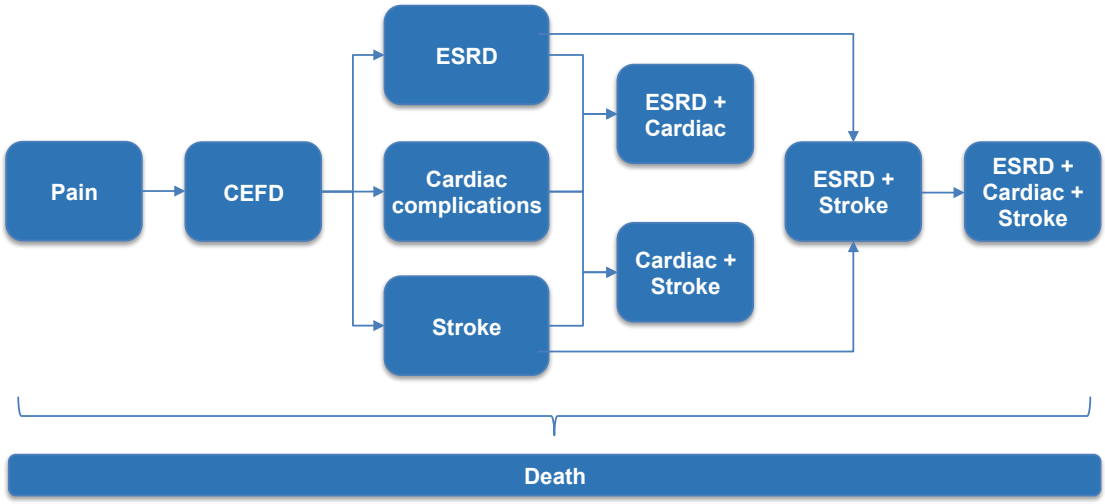
Therefore, the chosen model is a Markov model as illustrated in Figure D12.1. The model tracks patients as they progress through a series of 10 mutually exclusive health states:

- Pain
- Clinically evident Fabry disease (CEFD)
- ESRD
- Cardiac complications
- Stroke
- ESRD and cardiac complications

- ESRD and stroke
- Cardiac complications and stroke
- ESRD, cardiac complications and stroke
- Death.

See section 12.1.6 for details of what symptoms and manifestations of Fabry disease are included in each health state.

Figure D12.1: Cost-consequence model structure



The model structure differs from that in Rombach et al., 2013 in that the symptoms state from Rombach has be relabelled as Clinically Evident Fabry Disease (CEFD) to represent patients that have symptoms of Fabry disease that have not yet progressed to ESRD, cardiac complications or stroke. The acroparesthesia state has been relabelled to Pain for simplicity and the Cerebrovascular accident state has been relabelled to Stroke.

Another difference to Rombach et al is that there can be no disease regression (i.e. backward transitions), whereas the Rombach et al. model allowed patients with ESRD to return to the CEFD state following a kidney transplant. Also in contrast to Rombach et al., an asymptomatic health state is not included since the modelled cohort will have been diagnosed and initiated on treatment at the start of the model and therefore have pain, CEFD or complications.

Progression through the health states is similar to that in Rombach et al., 2013, such that patients progress from pain to CEFD; from CEFD to a single complication state; from a single complication state to double complications; and from a double complication state to the triple complication state. It is also possible to transition to death from each health state.

An overview of the properties of the model can be seen in Table D12.1.

Table D12.1: Overview of cost-consequence model properties

Aspect	Details	Justification
Analytical method	Markov model	Most appropriate method for modelling long-term chronic conditions with dynamic deterioration in health status
Software used	Microsoft Excel®	Transparent and widely used software
Model perspective(s)	• Base case: NHS & PSS • Sensitivity analysis: Societal	All relevant perspectives and consistent with the reference case (National Institute for Health and Care Excellence, 2013)
Cycle length	1 year	Consistent with Rombach et al (2013)
Mid-cycle correction	Applied to costs and benefits	In accordance with the reference case (National Institute for Health and Care Excellence, 2013)
Discounting	3.5% costs and benefits	In accordance with the reference case (National Institute for Health and Care Excellence, 2013)
Time horizon	Lifetime – achieved by simulating the patient population up to age 100 years from the baseline of 48 years (in line with ATTRACT study)	In accordance with the reference case (National Institute for Health and Care Excellence, 2013) due to the chronic nature of Fabry disease
Patient population	Fabry disease patients with amenable mutations who are at least 16 years old and have no ESRD at baseline	Expected licensed indication and in line with scope
Health states	• Pain • Clinically evident Fabry disease (CEFD) • End stage renal disease (ESRD) • Cardiac complications • Stroke • ESRD and cardiac complications • ESRD and stroke • Cardiac complications and stroke • ESRD, cardiac complications and stroke • Death	Based on the structure of a recent cost-effectiveness model for ERT by Rombach et al. (2013) that allows differentiation of the consecutive phases of Fabry disease with some re-labelling of states to better reflect the stages of the disease
Comparator	ERT	The scope includes agalsidase alfa and agalsidase beta, which are ERTs that are considered to be clinically equivalent (see Section 8.2). In line with the definition of the comparator in the ATTRACT study and other published sources of data used for the cost-

Aspect	Details	Justification
		consequence model, the comparator is ERT, rather than specifically agalsidase alfa or agalsidase beta. Estimated market shares of 70% agalsidase alfa and 30% agalsidase beta are used to generate weighted average costs for ERT, based on clinical expert opinion.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

A Markov model was chosen, as it is the most appropriate method for modelling long-term chronic conditions with dynamic deterioration in health status.

As detailed in section 6.1, Fabry disease has a progressive course, with the number and severity of symptoms and the number of organ systems progressively increasing over time (Kes et al., 2013; Thomas and Hughes, 2014; Sivley, 2013; Mehta et al., 2004; Kusano et al., 2014; Germain, 2010):

- Progressive renal impairment is a prominent feature of Fabry disease. Renal failure is the primary cause of death in untreated patients who do not receive chronic haemodialysis or renal transplantation (Pisani et al., 2014; Mahmud, 2014; Germain, 2010).
- Cardiac symptoms are reported in 40-60% of patients with Fabry disease, with onset generally in the third to fourth decades (El-Abassi et al., 2014; Germain, 2010). That is, patients with Fabry disease experience serious cardiac disease far earlier than individuals in the general population. Overall, cardiovascular disease is one of the leading causes of reduced life expectancy in untreated patients with Fabry disease (Germain, 2010).
- Early cerebrovascular disease is a common complication of adult patients with Fabry disease. Manifestations include headaches, vertigo, and dizziness, as well as more serious conditions such as transient ischemic attacks (TIAs), ischemic strokes, and vascular dementia (El-Abassi et al., 2014; Sivley, 2013; Germain, 2010). In an analysis of the Fabry Outcome Survey, the frequency of stroke was about 12 times greater in males aged 25 to 44 compared to the general population (Mehta and Ginsberg, 2005).

Since cardiac disease, renal disease, and stroke are the most debilitating symptoms of Fabry disease (see Figure B6.1), these form the basis of the model health state structure, as they are the greatest drivers of costs and quality of life impact. Neurological pain is the most common early feature of Fabry disease and is therefore an important early health state. These primary symptoms (pain, cardiac disease, renal disease, and stroke) were therefore explicitly modelled.

Other common symptoms of Fabry disease are captured implicitly rather than explicitly and include gastrointestinal symptoms (although this is more frequent in children than adults and migalastat is indicated for patients aged 16 and over so gastrointestinal are not considered to be a primary symptom to be included in the model), skin manifestations and ocular symptoms.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table D12.2: List of assumptions in the model

Aspect of model	Assumption	Justification
Model structure	Treatment with ERT or migalastat decreases the probability of transitioning to a worse disease state	Since ERT or migalastat cannot reverse end-organ damage that has already occurred and clinical data shows ERT can stabilise organ function, it is expected that patients being treated with ERT will not improve thus will not transition back to a healthier disease states (also in line with evidence from Rombach et al (2013a)).
Market share	Agalsidase alfa: 70%; agalsidase beta: 30%	Clinical expert opinion
Treatment	ERT and migalastat are equivalent in terms of efficacy	Detailed in Section 8.2. Conservative assumption given ATTRACT outcomes suggesting potential benefit of migalastat over ERT in LVMi reduction and composite endpoint.
Treatment	No discontinuation of migalastat	Clinical trial data supports this assumption.
Treatment	When patients discontinue treatment, they are assumed to switch to no treatment	Approach taken for simplicity and transparency of decision-making. In practice, if a patient did discontinue from migalastat, they would likely switch to ERT (and vice-versa) but model complexity would need to increase in order to capture the costs and benefits associated.
Acute events	The number of acute events observed in UK population and recorded in NHS reference costs is representative of Fabry patients e.g. admissions for white matter lesions accounted for 50.9% of the total NHS admissions for white matter lesions, left ventricular hypotrophy or chronic kidney disease (stage 1-4), so it is assumed that 50.9% of patients with Fabry disease entering the CEFD health state will be admitted for white matter lesions.	Necessary assumption due to a lack of clinical data on specific events in Fabry patients.
Clinical data	Contact with health care workers from Dutch cohort representative of UK clinical practice	Lack of specific UK resource use data for patients with Fabry disease.
Treatment costs	It is assumed that there is a discount of 3% on the cost of	NHS England has tendered a national contract for ERT that includes a confidential discount. Sensitivity analysis

Aspect of model	Assumption	Justification
	ERT to the NHS.	is presented varying this discount between 0% and 7%.
Treatment costs	Adherence to treatment is assumed to be 100%	Given the chronic and devastating nature of Fabry disease, it is expected that all patients will remain adherent to treatment. Evidence in other disease areas suggests that patients are more adherent to oral formulations (Agashivala et al., 2013). Therefore, in clinical practice, is expected that patients will be more adherent to migalastat than ERT because it is an oral treatment, but a conservative assumption has been made that both treatments have equal compliance.
Administration costs	50% of patients require a nurse to deliver ERT infusions, while the remaining 50% of patients self-administer or have infusions administered by an informal caregiver and only receive one nurse visit per year	Clinical expert opinion.
Administration costs	The cost of homecare for ERT infusions is £200	The cost of homecare, in particular for the delivery/collection of medication and disposables associated with infusions has been contracted by NHS England under a confidential national tender. Clinical experts have estimated the cost of £200.

12.1.6 Define what the model's health states are intended to capture.

The model heath states are intended to capture the disease progression of an average patient from diagnosis through to death. This includes all points in the disease that have a substantial cost and quality of life impact. Outcomes are captured by each health state representing a category of complications that occur with Fabry disease. Within each health state there is a range of possible events, and the distribution of these contribute to the cost associated with each state. Events included in each health state are shown in Table D12.3.

Table D12.3: Events included in each health state

Health state	Complication
Pain	Neuropathic pain
CEFD	White matter lesions
	Left ventricular hypotrophy
	Chronic kidney disease (stage 1-4)
ESRD	Chronic kidney disease (stage 5)
Cardiac complications	Atrial fibrillation
	Rhythm disturbance requiring hospitalisation
	Pacemaker
	Cardiac congestion requiring hospitalisation
	Myocardial infarction
	Percutaneous coronary Intervention
	Implantable cardiac defibrillator
	Coronary artery bypass graft
Stroke	Stroke

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Please see Table D12.1.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-consequence analysis.

Demographics

The model allows selection from two starting populations: the first considers the characteristics of the population randomised in the ATTRACT study and the second is a hypothetical cohort of newly-diagnosed patients with Fabry disease from 16 years of age.

The patient demographics at model baseline in the base case analysis were taken from the ATTRACT study. The mean age at baseline was 48 years. Given that the model is being evaluated over a lifelong time horizon with a maximum age of 100 years, this equates to a 52-year time horizon. In the scenario analysis of a cohort with baseline age 16 years, the time horizon is equivalent to 84 years.

Clinical expert opinion suggests that half of treated patients with Fabry disease are male. The average weight by age group and gender is taken from the Health Survey for England (Health & Social Care Information Centre, 2014) (Table D12.4). In line with clinical expert opinion, Fabry disease patients are assumed to be the same weight as the general population.

Table D12.4: Average weight by age group and gender

Age	Males Mean (Kg)	Females Mean (Kg)
16-24	75.13	64.85
25-34	83.01	70.35
35-44	86.37	72.01
45-54	87.7	74.01
55-64	88.67	74.31
65-74	83.48	72.1
75+	80.91	67.69

A scenario analysis is conducted in which the average patient weight is obtained from ATTRACT (74.1kg). Note that this scenario does not account for variations with age or gender.

Baseline characteristics

The distribution of the patients over the health states at baseline was based on patients' medical history upon enrolment to the ATTRACT study (Table 14.1.7 of the ATTRACT CSR). Medical history was used rather than baseline characteristics because the baseline characteristics were not recorded at the level of detail required for this analysis. This may lead to an overestimation of patients in the more severe states (e.g. cardiac complications) because although patients may have had a medical history of a complication, it may have been resolved by the time they were enrolled in the clinical trial.

In line with the symptoms/complications that the health states capture (see Table D12.3), an approximation of the patients in each health state at baseline was calculated (Table D12.5). It should be noted that absolute numbers of patients with each medical history item were recorded and where states are made of multiple items (e.g. CEFD state is white matter lesions, left ventricular hypotrophy and chronic kidney disease (stage 1-4)) there is likely to be double-counting as some patients will have more than one of these symptoms.

Table D12.5: Distribution of patients between health states at the start of the model in base case

Health State	Proportion of patients in state at baseline	Source
Pain	14.0%	All other patients
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)

Note: percentages may appear to sum incorrectly due to rounding

The baseline health state distribution of a cohort starting at age 16 years was assumed to be 80% in the pain state and the remaining 20% in the CEFD state, based on clinical expert opinion.

Transition probabilities

As stated in Table D12.2, the base case cost-consequence model the treatment effect of migalastat is considered to be equal to the treatment effect of ERT on reducing disease progression i.e. there is no difference in the transition probabilities for migalastat and ERT. However, this may be a conservative assumption since in ATTRACT the LVMi decreased significantly in patients switched from ERT to migalastat (whilst remaining stable in patients remaining on ERT) and rates of renal, cardiovascular, and cerebrovascular events experienced by patients switched from ERT to migalastat compared favourably with those experienced by patients who remained on ERT (29% vs 44%, respectively) (ATTRACT Draft Manuscript). Consequently, the conservative assumption that migalastat and ERT are clinically equivalent is applied in the base case but scenarios are explored in which migalastat is associated with more favourable transition probabilities than ERT.

The annual probabilities of moving between each health state are taken from Rombach et al., 2013. These values were determined from a Dutch cohort of Fabry patients. Untreated transition probabilities were determined using data from the period prior to the introduction of ERTs. Kaplan-Meier survival analysis was used to derive a median time to transition to the next state. A relative risk reduction due to the duration of treatment with ERT within each health state was then applied to the untreated transition probability to generate probability of transitions on ERT. The transition matrices for the treated and untreated male patients with Fabry disease are given in Table D12.6 and Table D12.7, respectively, and similarly for female patients with Fabry disease in Table D12.8 and Table D12.9.

Table D12.6: Transition matrix for migalastat- or ERT-treated male patients with Fabry disease

	Pain	CEFD	ESRD	Cardiac complications	Stroke	ESRD & cardiac	Cardiac & stroke	ESRD & stroke	ESRD, cardiac & stroke	Death
Pain	0.929-m_{AG}	0.0711	0	0	0	0	0	0	0	m_{AG}
CEFD	0	0.986	0.002	0.009	0.003	0	0	0	0	0.001
ESRD	0	0	0.974	0	0	0.009	0	0.006	0	0.017
Cardiac complications	0	0	0	0.974		0.005	0.008	0	0	0.0134
Stroke	0	0	0	0	0.974	0	0.009	0.005	0	0.012
ESRD & cardiac	0	0	0	0	0	0.455	0	0	0.138	0.407
Cardiac & stroke	0	0	0	0	0	0	0.455	0	0.138	0.407
ESRD & stroke	0	0	0	0	0	0	0	0.455	0.138	0.407
ESRD, cardiac & stroke	0	0	0	0	0	0	0	0	0.593	0.407

Table D12.7: Transition matrix for male patients with Fabry disease after discontinuation of treatment

	Pain	CEFD	ESRD	Cardiac complications	Stroke	ESRD & cardiac	Cardiac & stroke	ESRD & stroke	ESRD, cardiac & stroke	Death
Pain	0.929-m_{AG}	0.071	0	0	0	0	0	0	0	m_{AG}
CEFD	0	0.984	0.002	0.010	0.003	0	0	0	0	0.001
ESRD	0	0	0.960	0	0	0.013	0	0.010	0	0.017
Cardiac complications	0	0	0	0.960		0.008	0.012	0	0	0.021
Stroke	0	0	0	0	0.960	0	0.015	0.007	0	0.019
ESRD & cardiac	0	0	0	0	0	0.455	0	0	0.138	0.407
Cardiac & stroke	0	0	0	0	0	0	0.455	0	0.138	0.407
ESRD & stroke	0	0	0	0	0	0	0	0.455	0.138	0.407
ESRD, cardiac & stroke	0	0	0	0	0	0	0	0	0.593	0.407

m_{AG}: background mortality as a function of age and gender

Table D12.8: Transition matrix for migalastat- or ERT-treated female patients with Fabry disease

	Pain	CEFD	ESRD	Cardiac complications	Stroke	ESRD & cardiac	Cardiac & stroke	ESRD & stroke	ESRD, cardiac & stroke	Death
Pain	0.898- m_{AG}	0.102	0	0	0	0	0	0	0	m_{AG}
CEFD	0	0.99- m_{AG}	0.002	0.006	0.002	0	0	0	0	m_{AG}
ESRD	0	0	0.974	0	0	0.009	0	0.006	0	0.011
Cardiac complications	0	0	0	0.974		0.005	0.008	0	0	0.013
Stroke	0	0	0	0	0.974	0	0.009	0.005	0	0.012
ESRD & cardiac	0	0	0	0	0	0.455	0	0	0.138	0.407
Cardiac & stroke	0	0	0	0	0	0	0.455	0	0.138	0.407
ESRD & stroke	0	0	0	0	0	0	0	0.455	0.138	0.407
ESRD, cardiac & stroke	0	0	0	0	0	0	0	0	0.593	0.407

Table D12.9: Transition matrix for female patients with Fabry disease after discontinuation of treatment

	Pain	CEFD	ESRD	Cardiac complications	Stroke	ESRD & cardiac	Cardiac & stroke	ESRD & stroke	ESRD, cardiac & stroke	Death
Pain	0.898- m_{AG}	0.102	0	0	0	0	0	0	0	m_{AG}
CEFD	0	0.988- m_{AG}	0.002	0.007	0.003	0	0	0	0	m_{AG}
ESRD	0	0	0.960	0	0	0.013	0	0.010	0	0.017
Cardiac complications	0	0	0	0.960	0	0.008	0.012	0	0	0.021
Stroke	0	0	0	0	0.960	0	0.015	0.007	0	0.019
ESRD & cardiac	0	0	0	0	0	0.455	0	0	0.138	0.407
Cardiac & stroke	0	0	0	0	0	0	0.455	0	0.138	0.407
ESRD & stroke	0	0	0	0	0	0	0	0.455	0.138	0.407
ESRD, cardiac & stroke	0	0	0	0	0	0	0	0	0.593	0.407

m_{AG}: background mortality as a function of age and gender

Background mortality is age- and gender-dependent and is taken from UK life tables (Office for National Statistics, 2014). Annual probability of death by single year age and gender are used. The model uses two life tables: that of individuals born in 1968 for the ATTRACT cohort (age of 48 in 2016), and that of individuals born in 2000 for the 16 year olds (age of 16 in 2016).

Patients are at risk of background mortality from all health states. Fabry-specific mortality can occur in all complication states (see Tables D12.6 to D12.9), as well as in the CEFD state for patients with classic Fabry disease. In health states where patients are at risk of both background and Fabry-specific mortality, only one mortality rate is applied in order to avoid double counting. In this instance, the model selects the maximum of the two.

Discontinuations

Discontinuation of treatment was observed in some clinical trials (Banikazemi et al., 2007) for ERTs at approximately 1% of patients per year. The discontinuations observed in clinical trials were associated with IARs, which according to clinical experts can be controlled in clinical settings with additional medications. Therefore, the model assumes a lower annual probability of discontinuation of 0.05% per annum with ERT.

Conversely, there were no discontinuations in ATTRACT with migalastat, except for two prior to randomisation due to withdrawal of consent (Amicus Therapeutics, 2015d). UK clinical experts have confirmed discontinuation in clinical practice is unlikely. Therefore, the model assumes no discontinuation with migalastat.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Migalastat and ERT are assumed to be effectively equivalent over the lifetime of the model. This is based on the clinical study that showed migalastat and ERT to be equally effective in stabilising renal and cardiac function over the 18 month study period of ATTRACT. In addition, recently reported data from the 12-month open-label extension phase of ATTRACT indicate that in patients switched from ERT, the renal and cardiac effects of migalastat observed following 18 months persist over 30 months (Bichet et al., 2016).

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Intermediate outcomes were not used in the model.

12.2.4 Were adverse events included in the cost-consequence analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The model includes the annual probability of treatment emergent adverse events (TEAEs) in the ERT and migalastat arms (Table D12.10) based on the ERT and migalastat arms of the ATTRACT trial (Table C9.28) adjusted for exposure. TEAEs that were reported in more than 10% of either the ERT or migalastat arms were considered for inclusion in the model. All serious adverse events occurring in ATTRACT were deemed unrelated to study drug (see Section 9.7.2).

Table D12.10: Annual probability of TEAEs

TEAE	ERT	Migalastat
Headache	18.80%	18.20%
Influenza	14.90%	9.90%
Dyspnoea	3.70%	7.90%
Upper respiratory tract infection	3.70%	7.90%
Urinary tract infection	7.40%	2.00%
Gastritis	7.40%	2.00%

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The following clinical experts were consulted during the development of the cost-consequence model for migalastat:

- Dr Chris Hendrickz - Department of Adults with Inherited Metabolic Disorders, Salford Royal Hospitals NHS Trust
- Dr Ana Jovanovic - Department of Adults with Inherited Metabolic Disorders, Salford Royal Hospitals NHS Trust
- Dr Derralynn Hughes - Royal Free London NHS Foundation Trust and University College London
- Two additional experts in UK specialist centres were also consulted but declined to be named in this assessment.

Dr Derralynn Hughes has the greatest number of patients with Fabry disease in the UK and acted as the key source of data referenced to clinical expert opinion. In particular, Dr Hughes was consulted regarding the appropriateness of using the published Dutch cost-effectiveness study as a basis for the model structure, transition matrices and some resource use estimates. Dr Hughes also provided patient demographics (% female, % receiving nurse infusion-administration) and costs (estimated ERT national discount, cost of homecare).

Dr Hendrickz and Dr Jovanovic provided ratification of patient weight, patient numbers and medications pre/post infusions via face-to-face meetings.

The two additional experts were consulted over the telephone using a framework that evaluated the clinical pathway and management of existing patients, patient demographics, insights into infusions and feedback on the trial data for migalastat (Amicus Therapeutics, 2016a). This data verified the demographic inputs for the model but did not provide specific inputs.

12.2.6 Summarise all the variables included in the cost-consequence analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

Table D12.11: Summary of clinical variables applied in cost-consequence model

Variable	Value	Range or 95% confidence interval	Source
Baseline patient characteristics			
Age	48 years	18 – 72 years	Table C9.7; Amicus Therapeutics, 2015b
% female	50%	0 – 100%	Mean from clinical expert opinion, range tested in sensitivity analysis
Weight	See Table D12.4	N/A	Health & Social Care Information Centre, 2014
Transition probabilities – treated males			
Pain > CEFD	0.0711	0.0019-0.2354	Rombach et al., 2013
CEFD > ESRD	0.0097	0.0003-0.0354	
CEFD > Cardiac	0.0020	0-0.0076	
CEFD > stroke	0.0034	0.0001-0.0127	
CEFD > death	0.0006	0-0.0021	
Transition probabilities – treated females			
Pain > CEFD	0.1018	0.0025-0.3781	Rombach et al., 2013
CEFD > ESRD	0.0071	0.0001-0.0275	
CEFD > Cardiac	0.0018	0-0.0072	
CEFD > stroke	0.0027	0.0001-0.0097	
Transition probabilities – treated males and females			
ESRD > ESRD & cardiac	0.0133	0.0004-0.0462	Rombach et al., 2013
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	0.0146	0.0003-0.062	
Stroke > stroke & cardiac	0.0070	0.0002-0.0266	

Variable	Value	Range or 95% confidence interval	Source
Stroke > death	0.0186	0.0005-0.0655	
Transition probabilities – untreated males			
Pain > CEFD	0.0711	0.0020-0.2409	Rombach et al., 2013
CEFD > ESRD	0.0017	0.0000-0.0059	
CEFD > Cardiac	0.0085	0.0002-0.0324	
CEFD > stroke	0.0029	0.0001-0.0108	
CEFD > death	0.0006	0.0000-0.0022	
Transition probabilities – untreated females			
Pain > CEFD	0.1018	0.0028-0.3216	Rombach et al., 2013
CEFD > ESRD	0.0016	0.0000-0.0065	
CEFD > Cardiac	0.0062	0.0002-0.0268	
CEFD > stroke	0.0024	0.0001-0.0093	
Transition probabilities – untreated males and females			
ESRD > ESRD & cardiac	0.0086	0.0002-0.0316	Rombach et al., 2013
ESRD > ESRD & stroke	0.0063	0.0002-0.0260	
ESRD > death	0.0109	0.0003-0.0425	
Cardiac > cardiac & ESRD	0.0050	0.0001-0.0186	
Cardiac > cardiac & stroke	0.0077	0.0002-0.0285	
Cardiac > death	0.0134	0.0003-0.0519	
Stroke > stroke & ESRD	0.0045	0.0001-0.0168	
Stroke > stroke & cardiac	0.0094	0.0002-0.0321	
Stroke > death	0.0120	0.0003-0.0397	
Transition probabilities – treated and untreated males and females			
2 complications > 3rd complication	0.1379	0.0216-0.3506	Rombach et al., 2013
2 complications > death	0.4068	0.1512-0.7009	
3 complications > death	0.4068	0.1327-0.6961	

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

As a multi-organ disorder, it is difficult to attribute clinical management costs to specific HRG codes within the PbR tariff. Details of the key costs for the treatment of complications, routine health care contacts and follow-up costs including the HRG codes from NHS reference costs can be found in Section 12.3.7.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Please see Appendix 17.1.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[3].

Please see Section 12.2.5.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The annual acquisition cost of migalastat is £210,000, which corresponds to 13 packs priced at £16,153.85.

The cost of agalsidase beta and agalsidase alfa were taken from the BNF (British National Formulary, 2015) and are shown in Table D12.12.

Table D12.12: Dosage and cost of ERT

	Vial size	Cost per vial	Dose per infusion (mg per kg)
Agalsidase beta	5 mg	£315.08	1
	35 mg	£2,196.59	
Agalsidase alfa	3.5 mg	£1,068.64	0.2

12.3.5 If the list price is not used in the de novo cost-consequence model, provide the alternative price and a justification.

NHS England has tendered a national contract for ERT that includes a confidential discount. In the base case analysis, it is assumed that this discount is 3%. Sensitivity analysis is presented varying this discount between 0% and 7%.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost consequence model. A suggested format is provided in tables D6

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Intervention costs

Table D12.13: Annual treatment and administration cost per patient with migalastat in cost-consequence model

Items	Value	Source
Price of the technology per pack of 14 tablets (28 days)	£16,153.85	
Administration cost	£0	N/A – migalastat is administered orally
Training cost	£0	N/A – migalastat is administered orally
Annual cost per patient	£210,000	

ERT acquisition costs

Agalsidase beta and agalsidase alfa are dosed dependant on weight. The average weight by age group and gender is detailed in Section 12.2.1. Clinical expert opinion suggests that of all the English patients receiving ERT, approximately 70% receive agalsidase alfa. The average per patient cost for per infusion, adjusting for this market share, is detailed in Table D12.14.

Table D12.14: Cost of ERT by age and gender

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 administration costs

ERT is associated with bi-weekly administration costs, which include:

- Delivery of medication and disposables associated with infusions to all patients
- Nurse visit to administer medication for some patients (some patients will be supported by informal caregivers)

- Cost of pre-infusion medications to reduce the likelihood and impact of infusion associated reactions.

The cost of homecare, in particular for the delivery/collection of medication and disposables associated with infusions has been contracted by NHS England under a confidential national tender. In the base case, it is assumed that the cost of this homecare is £200 per bi-weekly infusion based on clinical expert opinion, equating to a cost per patient per year of £5,200.

According to clinical experts, 50% of patients require a nurse to deliver the infusion; while the remaining 50% of patients self-administer or have infusions administered by an informal caregiver and therefore only receive one nurse visit per year. Nurse visit costs were approximated using the clinical nurse specialist cost of £91 per hour (patient contact time) provided in the Unit Costs of Health and Social Care 2015 (Curtis and Burns, 2015). In line with the SPC and suggested dosing rate, an infusion time of two hours is assumed for agalsidase beta and 40 minutes for agalsidase alfa. It is also estimated that an additional 45 minutes per infusion is required for preparation and monitoring. Therefore:

- For agalsidase beta, 2-hour infusion + 45 minutes from pre/clean-up = £250.
- For agalsidase alfa, 40-minute infusion + 45 minutes from pre/clean-up = £129.

Assuming a 70% market share for agalsidase alfa as advised by clinical experts, this equates to an average per infusion nurse visit cost of £165.30.

Annual treatment and administration costs of ERT are shown in Table D12.15.

Table D12.15: Annual treatment and administration cost per patient with ERT in cost-consequence model

Items	Value	Source
Annual acquisition cost per male patient by age		
16-24	£132,335.44	List price from BNF Dosing from SPCs (Shire, 2006; Genzyme Therapeutics, 2014) Discount on price assumed Weight from Health Survey for England 2014
25-34	£134,719.34	
35-44	£137,103.23	
45-54	£155,969.00	
55-64	£155,969.00	
65-74	£134,719.34	
75+	£134,719.34	
Annual acquisition cost per female patient by age		
16-24	£106,385.85	List price from BNF Dosing from SPCs (Shire, 2006; Genzyme Therapeutics, 2014) Discount on price assumed Weight from Health Survey for England 2014
25-34	£129,951.55	
35-44	£129,951.55	
45-54	£129,951.55	
55-64	£129,951.55	
65-74	£129,951.55	
75+	£108,769.75	
Administration		
Cost of homecare	£200.00	Clinical expert opinion (true price is

		confidential)
Cost of nurse visit for ERT	£165.30	Derived using PSSRU 2015
Proportion of patients receiving nurse-administration	50%	Clinical expert opinion
ERT administration cost per infusion	£285.83	
Annual ERT administration cost	£7,431.55	
Pre-infusion medication cost per infusion		
Paracetamol – eight 500 mg tablets per day for 3 days	£0.04	£0.74 for 100 500mg tablets (British National Formulary, 2015); for each infusion, 20% of patients receive 8 tablets per day for 3 days (clinical expert opinion)
Chlorpheniramine (Piriton) – six 4 mg tablets for 3 days	£0.21	£3.57 for 60 4mg tablets (British National Formulary, 2015); for each infusion, 20% of patients receive 6 tablets per day for 3 days (clinical expert opinion)
Methylprednisolone – one 4 mg tablet per day for 3 days	£0.01	£6.19 for 30 4mg tablets (British National Formulary, 2015); for each infusion, 5% of patients receive 1 tablet per day for 3 days (clinical expert opinion)
ERT pre-infusion cost per infusion	£0.26	
Annual administration cost per patient	**£7,438.31**	

Health-state costs

12.3.7 If the cost-consequence model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost-consequence model.

Acute event costs

Acute event costs are applied once as patient transition into each state. The cost of each acute event included in the health states is provided in Table D12.16. Unit costs were taken from NHS reference costs for the year 2014–15 (Department of Health, 2015). The costs shown are derived from a range of codes representing different severity for each event, weighted by the number of events (activity) reported.

Table D12.16: Cost for acute events

Health state	Complication	Cost	NHS reference cost code	Weights applied
CEFD	White matter lesions	£1,630.30	AA25C-G Non-elective long and short stay	50.9%
	Left ventricular hypertrophy	£1,652.47	BB14A-E Non-elective long and short stay	48.7%
	Chronic kidney disease (stage 1-4)	£1,482.02	LA08P+N Elective inpatient	0.3%
	Total	*£1,639.03*		
ESRD	Chronic kidney disease (stage 5)	£3,062.87	LA08K-M Elective inpatient	100%
Cardiac Complications	Atrial fibrillation/ Rhythm disturbance requiring hospitalization	£903.14	EB07A-E Non-elective long and short stay	18.4%
	Pacemaker	£3,029.82	EY08A-E Elective Inpatient	1.2%
	Cardiac congestion requiring hospitalization	£1,895.14	EB03A-E Non-elective long and short stay	32.0%
	Myocardial infarction	£1,382.74	EB10A-E Non-elective long and short stay	27.9%
	Percutaneous coronary intervention	£4,691.36	EY23A-C Elective Inpatient	0.1%
	Implantable cardiac defibrillator	£13,313.50	EY02A+B Elective Inpatient	0.6%
	Coronary artery bypass graft	£9,472.44	AD28A-C Elective Inpatient	1.4%
	Total	*£1,578.13*		
Stroke	Stroke	£2,906.77	AA35A-F Non-Elective Inpatients long and short stay	100%

Follow-up costs

Follow-up costs for Fabry disease management are composed of ambulatory care, diagnostics, imaging and laboratory testing. Ambulatory care comprises annual visits to health care workers at a frequency that varies by health state. The frequency of visits is taken from Rombach et al. and are, therefore, reflective of the Dutch setting. It is assumed that these would not differ significantly in the UK. UK-specific unit costs were applied to each resource. Frequency of visits by health state is shown in Table D12.17.

Table D12.17: Annual frequency of health care visits by health state

Health care contact	Pain	CEFD	Single complication	Multiple complications
General practitioner	2.10	3.50	3.70	4.80
Physiotherapist	5.40	5.60	18.50	8.80
Psychologist/psychiatrist	3.70	1.50	0.10	0.00
Social worker	0.20	0.30	0.40	0.30

The cost for a single visit is based on the cost per hour in the UK and the duration of each contact according to the PSSRU (Curtis and Burns, 2015). The duration of an average general practitioner (GP) visit is 11.7 minutes at the surgery, and the duration of an average physiotherapy visit is one hour. Durations for other visits not reported were assumed to be an hour (Table D12.18).

Table D12.18: Cost per visit for health care contacts

Health care contact	Cost per hour (£)	Duration (hours)	Cost per visit
General practitioner	225	0.195	£43.88
Physiotherapist	36	1	£36.00
Psychologist/psychiatrist	52	1	£52.00
Social worker	57	1	£57.00

The frequency of diagnostic, laboratory and imaging tests for all patients with Fabry disease were taken from the Adult Fabry Disease Standard Operating Procedure 2013 (Hughes et al., 2013a). Unit costs are from NHS reference costs for the year 2014–15 for direct access diagnostic and pathology services and diagnostic imagining (Department of Health, 2015). Frequency and costs of these procedures are shown in Table D12.19. Note that the assay for alpha-galactosidase A antibodies is unlikely to be required for migalastat but for simplicity, this test was included in both the migalastat arm and the ERT arm.

Table D12.19: Frequency and costs of follow-up procedures for managing Fabry disease

Procedure	Annual frequency	Unit cost
Full blood count (haematology)	2.00	£3.00
Urine test (albumin/creatinine)	2.00	£6.99
ECG	3.00	£52.13
Liver function test	2.00	£8.33
Fasting lipid profile	2.00	£3.57
2D echocardiography with Doppler	1.00	£57.07
Glomerular filtration rate	1.00	£1.19
24 hour urine protein/creatinine	1.00	£6.99
Exercise testing	1.00	£87.52
Renal USS	1.00	£59.90
MRI	0.50	£163.87
Audiogram	1.00	£61.31
Plasma CTH	1.00	£1.19
Assay for alpha-galactosidase A antibodies	1.00	£5.49

Abbreviations: CTH, globotriaosylceramide; ECG, electrocardiogram; MRI, magnetic resonance imaging; USS, ultrasound

Follow-up costs for each complication type were also applied annually to all patients in that health state. These costs are shown in Table D12.20.

Table D12.20: Follow-up costs by complication

Health state	Cost details	Annual frequency	Unit cost (£)	Source
Cardiac	Cost per patient with coronary heart disease in the UK 2015	1	627.09	(Bhatnagar et al., 2015) [2,307,076 patients with coronary heart disease in the UK cost £1,430.8 in 2012/13 budget year] Inflated to 2015 with PSSRU data (Curtis and Burns, 2015)
ESRD	Dialysis at a frequency of 156 sessions per year	156	165.39	(Hughes et al., 2013a) Dialysis assumed to be needed 3 times a week National Schedule of Reference Costs (Department of Health, 2015) - Renal dialysis
Stroke	Annual cost of post-acute care for stroke survivors	1	415.62	(Luengo-Fernández et al., 2006) Inflated to 2015 with PSSRU data (Curtis and Burns, 2015)

The total costs per health state are summarised in Table D12.21.

Table D12.21: List of health states and associated costs in the cost-consequence model

Health states	Items	Value	Reference
Pain	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£490.35	Table D12.17, Table D12.18
CEFD	Hospitalisation	£1,630.30	Table D12.16
	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£450.28	Table D12.17, Table D12.18
ESRD	Hospitalisation	£3,062.87	Table D12.16
	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£856.36	Table D12.17, Table D12.18
	Complication follow-up costs	£25,800.84	Table D12.20
Cardiac complications	Hospitalisation	£1,578.13	Table D12.16
	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£856.36	Table D12.17, Table D12.18
	Complication follow-up costs	£627.09	Table D12.20
Stroke	Hospitalisation	£2,906.77	Table D12.16
	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£856.36	Table D12.17, Table D12.18
	Complication follow-up costs	£415.62	Table D12.20
ESRD + Cardiac	Hospitalisation	£4,641.00	Table D12.16

	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£544.52	Table D12.17, Table D12.18
	Complication follow-up costs	£26,427.93	Table D12.20
Cardiac + Stroke	Hospitalisation	£4,484.90	Table D12.16
	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£544.52	Table D12.17, Table D12.18
	Complication follow-up costs	£26,216.46	Table D12.20
ESRD + Stroke	Hospitalisation	£5,969.64	Table D12.16
	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£544.52	Table D12.17, Table D12.18
	Complication follow-up costs	£627.09	Table D12.20
ESRD + Cardiac + Stroke	Hospitalisation	£7,547.77	Table D12.16
	Diagnostic, laboratory and imaging tests	£562.76	Table D12.19
	Healthcare contacts	£544.52	Table D12.17, Table D12.18
	Complication follow-up costs	£26,843.55	Table D12.20

Adverse event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost-consequence model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The costs of AEs were based on drug costs and health care resource use assumed to be generated by each specific AE. The NHS patient website was used as a guidance as to how to manage these relatively minor events. Costs for each AE are shown in Table D12.22.

Table D12.22: List of adverse events and summary of costs included in the cost-consequence model

Adverse events	Items	Value	Reference
Headache	**Technology**		£0.74 for 100 500mg tablets (British National Formulary, 2015)
	Paracetamol for 1 day	£0.06	
	Total	**£0.06**	
Influenza	**Technology**		Pseudoephedrine SUDAFED, £2.04 for 12 tablets of 60mg each. Assume 4 tablets a day (British National Formulary, 2015)
	Decongestant for 5 days	£3.40	
	Staff		
	1 GP visit	£43.88	See Table D12.18
	Total	**£47.28**	
Dyspnoea	**Staff**		

	1 GP visit	£43.88	See Table D12.18
	Total	**£43.88**	
Upper respiratory tract infection	**Technology**		£0.74 for 100 500mg tablets (British National Formulary, 2015)
	Paracetamol for 3 days	£0.18	
	Staff		
	1 GP visit	£43.88	See Table D12.18
	Total	**£44.06**	
Urinary tract infection	**Technology**		£1.57 for 21 capsules of 500mg. Dosage 3g then 3g after 12 hours (British National Formulary, 2015)
	Short course of amoxicillin	£0.90	
	Staff		
	1 GP visit	£43.88	See Table D12.18
	Total	**£44.78**	
Gastritis	**Technology**		Mezzopram, £9.86 for 28 tablets of 20mg. Assume 20mg once daily (British National Formulary, 2015)
	Omeprazole for 3 days	£1.05	
	Staff		
	1 GP visit	£43.88	See Table D12.18
	Total	**£44.93**	

Abbreviations: BNF, British National Formulary; GP, general practitioner

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Productivity

The annual loss of earnings due to ERT infusions for patients and caregivers is based on an average wage of £13.14 per hour. This value is derived from ONS labour market statistics, which gives an average wage of £493 per week (total pay), adjusted to a 37.5-hour week (Office for National Statistics, 2015a).

For the employment rate of patients with Fabry disease, a study by Cole et al., 2007 was used that showed that 59% of 184 patients with Fabry disease with a mean age of 44 years were employed. For carers, the general population employment rate for 16–64 year olds is used, as carers are assumed to be between 16 and 64 years of age. It is assumed that 2 hours of work are lost per infusion for both the patient and the carer and that 50% of patients have a carer. Annual productivity losses are shown in Table D12.23.

Table D12.23: Productivity loses for patients and carers

Parameter	Cost / unit	Source
Hourly Earnings	£13.14	(Office for National Statistics, 2015b) [Table 15]
Patient		
Number of hours lost per infusion	2	Based on infusion time used in administration cost calculations
Proportion working full time	59%	Cole et al., 2007
Annual Productivity loss	**£403**	
Caregiver		
Proportion of patients with a caregiver	50%	Clinical expert opinion
Number of hours lost per infusion	2	Assumed equal to hours lost per patient
Proportion working full time	73.9%	(Office for National Statistics, 2015b) [Table 1]
Annual Productivity loss	**£252**	

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Please see section 14.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-consequence analysis.

Scenario analyses to investigate specific model assumptions inputs were conducted as follows.

1. *Price of ERT decreased by 0%, 5% and 7% to account for potential confidential discounts offered through a national tender*
2. *Utilities obtained from alternative literature sources (Miners et al., 2002; Gold et al., 2002) (see Section C10.3)*
3. *Reduced efficacy of ERT due to antibody formation*

   To simulate the reduced efficacy resulting from the formation of neutralising antibodies, a proportion of treated patients were artificially switched to untreated transition probabilities, while still accruing treatment costs.

   The draft Summary of Product Characteristics of agalsidase alfa states that antibodies have been found to appear following 3–12 months of treatment, and that in one study 17% of agalsidase alfa-treated patients were found to be antibody positive after 12 to 54 months of therapy (Shire, 2006). It is assumed that 20% of patients with antibodies would have neutralising antibodies. The long-term clinical impact of neutralising antibodies in the treatment of patients with Fabry disease are unknown but recent data suggest worse control of symptoms in patients with agalsidase antibodies present (Lenders et al., 2015). A 0.034 (=17%*20%) event rate over 54 months equates to an annual probability of switching from treated transition probabilities to untreated transition probabilities of 0.77%. This probability is only applied during the first 5 years of the model.
4. *Considering a cohort from 16 years of age in line with the minimum age at which a patient can receive migalastat*

   In this scenario, the baseline health state distribution was assumed to be 80% Pain and 20% CEFD, in line with clinical expert opinion.
5. *Using weight observed in clinical trial (74.1kg, not stratified by age or gender) rather than general population*
6. *Societal perspective to incorporate productivity losses associated with infusions*
7. *Applying a relative risk of 66% to transition probabilities of progressing to single, double or triple complications for migalastat based on secondary endpoint of composite clinical outcome observed in ATTRACT*
8. *Reduced time horizon to 20 years*
9. *Used alternative disutilities relating to infusions from DCE*
   - *Including full surveyed population (not specifically excluding the 53 people that failed the response check)*
   - *Including disutilities for all attributes surveyed (mode of administration, infusion reactions, headaches (both ERT and migalastat) and antibodies)*

- *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. *Equal market share between ERTs i.e. 50% agalsidase alfa and 50% agalsidase beta*

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

One-way deterministic sensitivity analysis (DSA) was conducted to assess the impact of each parameter on the difference in discounted QALYs with migalastat compared to ERT, and on the difference in total discounted cost. Variables included in the DSA are shown in Table D12.24.

A probabilistic sensitivity analysis (PSA) was run using 1,000 Monte Carlo Markov Chain simulations. Values for each simulation were selected from their distribution based on either the 95% confidence interval or standard error as shown in Table D12.25.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

The upper and lower 95% CI of each of the transition probabilities used in the one-way sensitivity analysis are detailed in Table D12.11. All other parameters are included in Table D12.24.

Table D12.24: Parameters varied in the one-way deterministic sensitivity analysis

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 AEs: ERT (± 20% of base case)	100%	80%	120%
Annual risk of AEs: migalastat (± 20% of base case)	100%	80%	120%
Discount rate for costs	3.5%	0%	6%
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

Table D12.25: Distributions used for variables in probabilistic sensitivity analysis

Variable	Distribution	Distribution parameters
Transition probabilities	Beta	95% CI from source
Discontinuation	Beta	95% CI assumed to be 20% variation
Adverse event probabilities	Beta	95% CI assumed to be 20% variation
Costs (acute event, follow-up, adverse event, healthcare contacts, ERT acquisition costs, ERT administration costs)	Lognormal	95% CI assumed to be 20% variation
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 a 20% variation was assumed)
Duration of adverse event	Lognormal	95% CI assumed
Productivity loss (patient and carer)	Lognormal	95% CI assumed to be 20% variation

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Constants such as the cycle length, frequency of ERT infusion, and cost of migalastat were excluded from the sensitivity analyses. ERT infusion costs were included in the analysis to account for variations in weight. Background mortality rates were also excluded from the analysis.

12.5 Results of de novo cost-consequence analysis

Section 12.5 requires the sponsor to report the de novo cost-consequence analysis results. These should include the following:

- benefits
- costs
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean results (costs, QALYs)
- results of the sensitivity analysis.

Clinical outcomes from the model

12.5.1 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over).

Due to the primary and secondary endpoints measured in the trial and the length of the trial compared to the slow progressive nature of Fabry disease, it is not possible to draw clear comparisons from the ATTRACT study to the model.

The time to onset of CEFD is identical for ERT and migalastat (Table D12.26). There is a negligible difference in the time to first complication (0.2 days). This is expected since both treatment options are assumed to have the same efficacy. There is a slight difference in the proportion experiencing cardiac events, ESRD and stroke due to the difference in discontinuation rates between ERT and migalastat. Patients are not expected to discontinue from migalastat whereas it is expected that 0.05% patients withdraw from ERT per year. This

means that migalastat patients will benefit from staying on treatment slightly longer and thus improved outcomes.

Table D12.26: Time to clinical outcomes predicted by the model

Outcome	Migalastat	ERT	Difference
Experiencing cardiac event	18.85%	18.88%	-0.04%
Experiencing stroke	10.60%	10.63%	-0.04%
Experiencing ESRD	14.08%	14.12%	-0.04%
Time to onset of CEFD (years)	1.48	1.48	0.00
Time to first complication (years)	24.18	24.18	0.00

12.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

There is no visible difference in the Markov trace for the migalastat and ERT simulations. As discussed above, this is expected since both treatment options are assumed to have the same efficacy, and only differ on discontinuation rates. Patients are not expected to discontinue from migalastat whereas it is expected that 0.05% patients withdraw from ERT per year. This means that migalastat patients will benefit from staying on treatment slightly longer and thus improved outcomes.

Figure D12.2: Proportion of migalastat-treated cohort in each health state over time

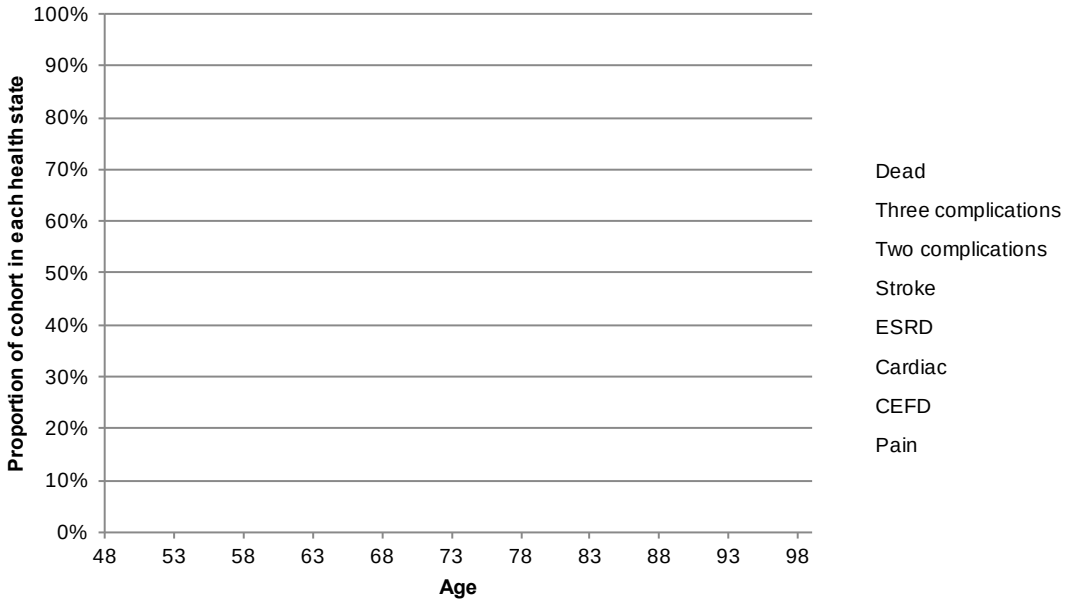
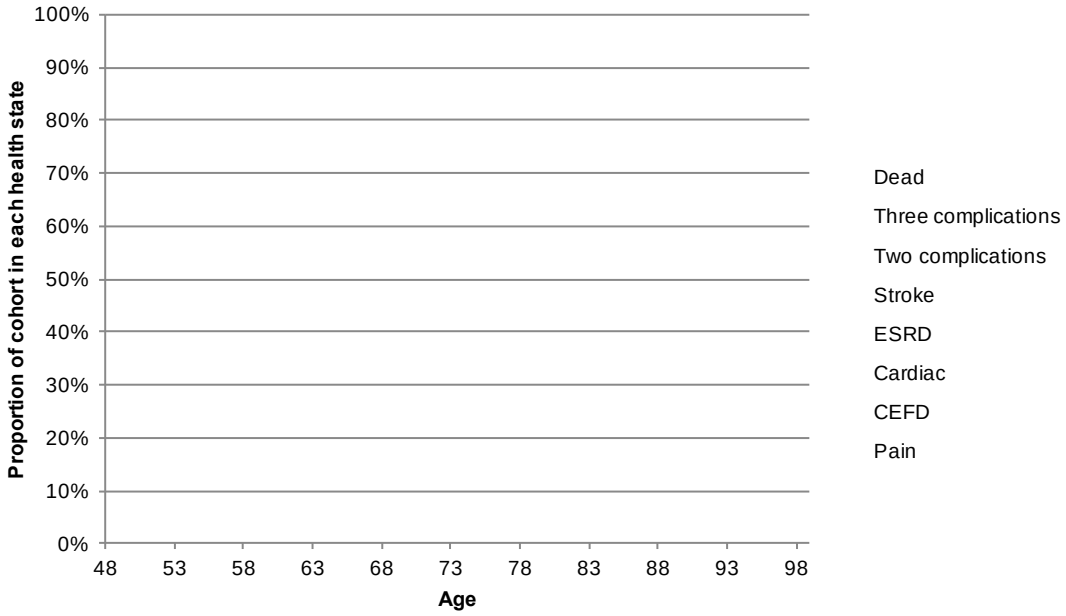


Figure D12.3: Proportion of ERT-treated cohort in each health state over time



12.5.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure D12.4: Accrual of health state QALYs over time with migalastat

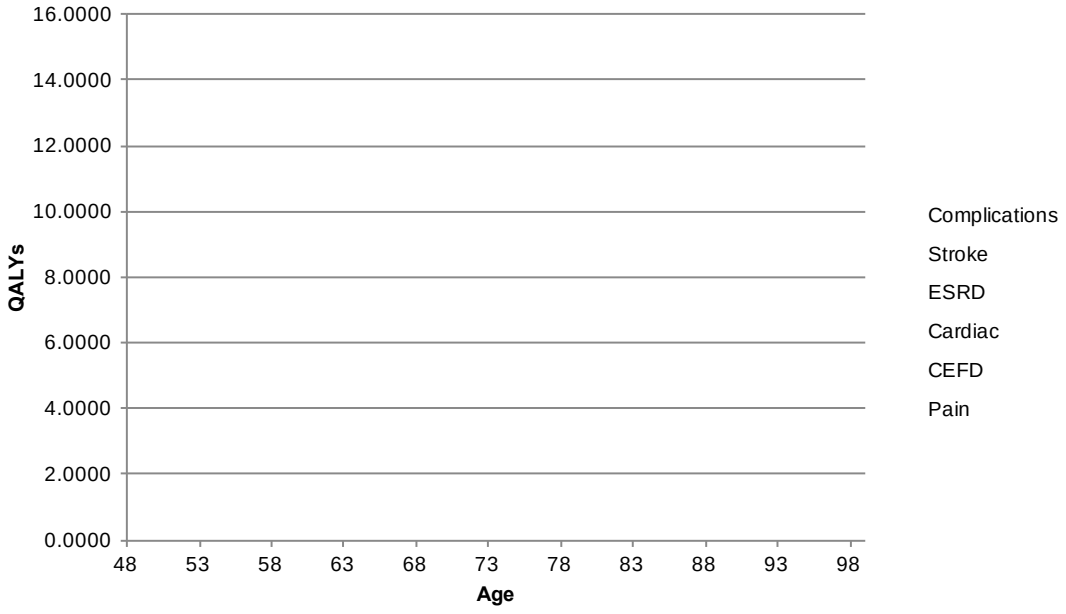
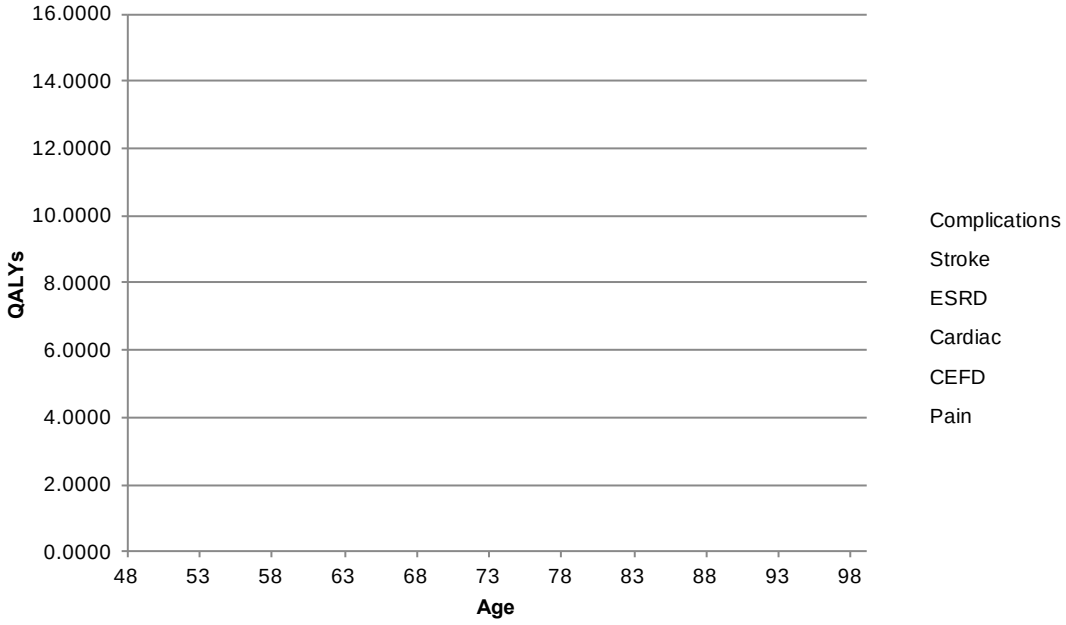


Figure D12.5: Accrual of health state QALYs over time with ERT



12.5.4 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Migalastat is associated with 0.98 more QALYs than ERT, discounted at a rate of 3.5% per annum (Table D12.27). As discussed above, both treatments are assumed to have the same efficacy, and only differ on discontinuation rates. Patients are not expected to discontinue from migalastat so benefit from staying on treatment slightly longer and thus very slightly improved outcomes (0.002 more QALYs) (Table D12.28). The key driver in the QALY gain with migalastat is from the treatment being an oral rather than infusion, which is associated with a lower patient burden in terms of convenience (Lloyd et al., 2016).

Note that the DCE study conducted by Amicus revealed very strong patient preferences not only for an orally administered treatment rather than an infusion, but also for fewer infusion-associated reactions / adverse events and avoidance of risk of neutralising antibodies. The base case analysis only factors in the disutility of administration, rather than these additional factors.

Table D12.27: Total QALYs and life years

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

Table D12.28: Summary of QALY gain by health state

Health state	Migalastat	ERT	Increment	Absolute increment	% absolute increment
Pain	0.82	0.82	0.00	0.00	0%
CEFD	9.40	9.40	0.00	0.00	0%
Single complication	3.98	3.98	0.00	0.00	0.2%
Multiple complications	0.13	0.13	0.00	0.00	0%
Infusions	0.00	-0.97	0.97	0.97	99.5%
Adverse events	-0.01	-0.01	0.00	0.00	0.3%
Total	**14.33**	**13.36**	**0.97**	**0.97**	**100%**

12.5.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Details of the disaggregated incremental QALYs and costs by health state are provided in Table D12.29. The disaggregated cost results (Table D12.30) show that approximately 9% of the incremental costs of migalastat are offset by the savings made on administration costs.

Table D12.29: Summary of health state costs

Health state	Cost migalastat	Cost ERT	Increment	Absolute increment	% absolute increment
Pain	530	530	0	0	0%
CEFD	5,710	5,710	0	0	0%
Complications	16,940	16,941	-1	1	100%
Total	**23,180**	**23,181**	**-1**	**1**	**100%**

Table D12.30: Summary of cost by type

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%**

Base-case analysis

12.5.6 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table D11.

Table D12.31 shows the lifetime costs per patient of ERT assuming a 3% national tender discount and migalastat at the list price. Migalastat is associated with an average lifetime cost of £4,024,050 per patient, while ERT is associated with £2,755,377 per patient, resulting in incremental costs of £1,268,674.

Table D12.31: Base-case results

	Total per patient cost (£)
Migalastat	4,024,050
ERT	2,755,377
Incremental	**1,268,674**

12.5.7 Report the total difference in costs between the technology and comparator(s).

At the list price for migalastat, the incremental cost between migalastat and ERT is £1,268,674 per patient.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost.

See Table D12.30.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

See Table D12.29.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event.

As shown in Table D12.30, AE costs are marginal in this model. Costs are not calculated per event but as an overall cost.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Results of the deterministic one-way sensitivity analysis as described in Table D12.24 are presented in Table D12.32. Figure D12.6 and Figure D12.7 illustrate the QALY results and cost results, respectively.

Results are sensitive to discount rates, transition probabilities for treated patients, discontinuation rates, the disutility of infusions and market shares of ERT. Results are insensitive to health state costs and utilities as well as all adverse event parameters.

Table D12.32: Results of deterministic one-way sensitivity analysis

Parameter	Incremental QALYs		% difference in QALYs		Incremental costs (£)		% difference in costs	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Base case	0.98		-		1,268,674		-	
% females	0.99	0.96	2%	-2%	1,497,191	1,040,157	18%	18%
Disease progression for untreated patients	0.98	1.00	0%	2%	1,283,631	1,263,456	1%	0%
Disease progression for treated patients	1.05	0.74	8%	-25%	1,367,237	949,620	8%	-25%
Discontinuation: ERT patients	0.98	0.89	1%	-9%	1,249,185	1,601,204	-2%	26%
Discontinuation: migalastat	0.98	0.97	0%	0%	-	1,209,778	-	-5%
Annual risk of AEs: ERT	0.97	0.98	0%	0%	1,268,738	1,268,610	0%	0%
Annual risk of AEs: migalastat	0.98	0.97	0%	0%	1,268,623	1,268,725	0%	0%
Discount rate for costs	-	-	-	-	2,506,801	879,540	98%	-31%
Discount rate for outcomes	1.82	0.70	86%	-28%	-	-	-	-
Acute event cost: CEFD	-	-	-	-	1,268,674	1,268,674	0%	0%
Acute event cost: cardiac complications	-	-	-	-	1,268,674	1,268,674	0%	0%
Acute event cost: ESRD	-	-	-	-	1,268,674	1,268,674	0%	0%
Acute event cost: stroke	-	-	-	-	1,268,674	1,268,674	0%	0%
Adverse event costs	-	-	-	-	1,268,687	1,268,661	0%	0%
Cost of health care provider contacts	-	-	-	-	1,268,673	1,268,674	0%	0%
Annual follow-up cost: all patients with Fabry disease	-	-	-	-	1,268,673	1,268,674	0%	0%
Annual follow-up	-	-	-	-	1,268,673	1,268,674	0%	0%

cost: cardiac complications								
Annual follow-up cost: ESRD	-	-	-	-	1,268,674	1,268,673	0%	0%
Annual follow-up cost: stroke	-	-	-	-	1,268,674	1,268,674	0%	0%
Utility: Pain	0.98	0.98	0%	0%	-	-	-	-
Utility: CEFD	0.98	0.98	0%	0%	-	-	-	-
Utility: ESRD	0.98	0.98	0%	0%	-	-	-	-
Utility: Cardiac complications	0.98	0.98	0%	0%	-	-	-	-
Utility: Stroke	0.98	0.98	0%	0%	-	-	-	-
Utility: Multiple complications	0.98	0.98	0%	0%	-	-	-	-
Disutility per infusion	1.12	0.85	14%	-13%	-	-	-	-
Disutility: headache	0.98	0.98	0%	0%	-	-	-	-
Disutility: influenza	0.98	0.98	0%	0%	-	-	-	-
Disutility: dyspnoea	0.98	0.98	0%	0%	-	-	-	-
Disutility: upper respiratory tract infection	0.98	0.98	0%	0%	-	-	-	-
Disutility: urinary tract infection	0.98	0.98	0%	0%	-	-	-	-
Disutility: gastritis	0.98	0.98	0%	0%	-	-	-	-
Market share of agalsidase alfa vs. agalsidase beta	0.98	0.98	0%	0%	1,453,363	1,189,521	15%	-6%
Duration of AE: headache	0.97	0.97	0%	0%	-	-	-	-
Duration of AE: influenza	0.98	0.98	0%	0%	-	-	-	-
Duration of AE: dyspnoea	0.98	0.98	0%	0%	-	-	-	-
Duration of AE: upper respiratory tract infection	0.98	0.98	0%	0%	-	-	-	-
Duration of AE: urinary tract infection	0.98	0.98	0%	0%	-	-	-	-
Duration of AE: gastritis	0.98	0.98	0%	0%	-	-	-	-

Figure D12.6: Tornado diagram illustrating difference in QALYs with migalastat

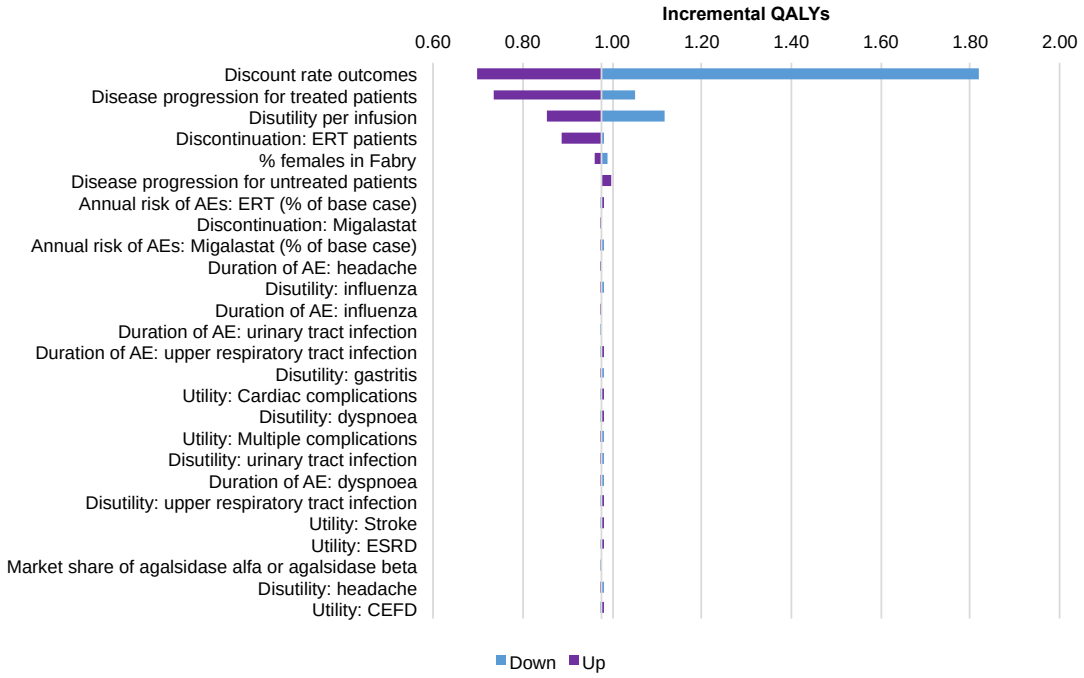
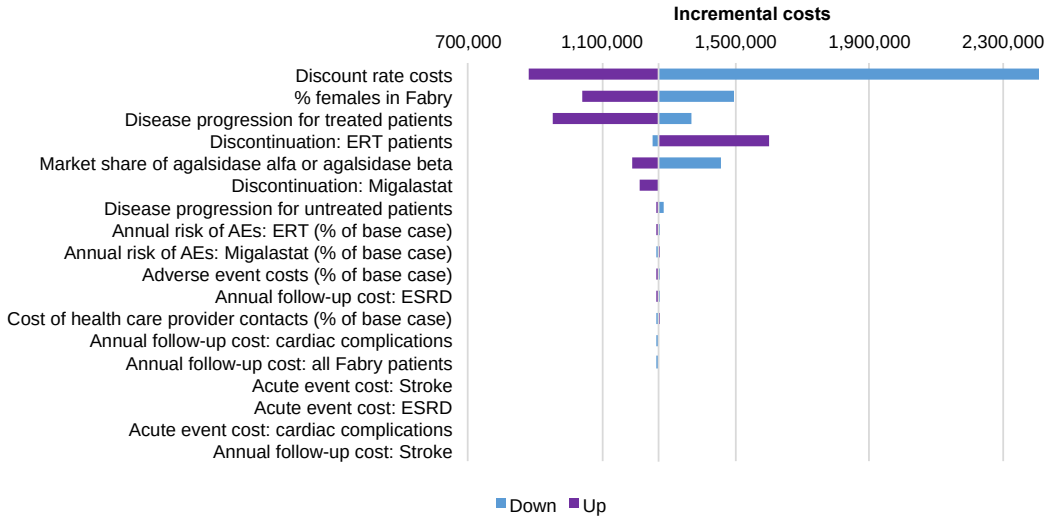


Figure D12.7: Tornado diagram illustrating difference in costs with migalastat



12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

NHS England has tendered a national contract for ERT that includes a confidential discount. In the base case analysis, it is assumed that this discount is 3%. To explore the range of possible discounts, the prices of both agalsidase alfa and agalsidase beta were decreased by 0%, 5% and 7% (Table D12.33).

Table D12.33: Scenario analysis: varying discount on ERT price

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%

The results of all other scenario analysis detailed in Section 12.4.1 are presented in Table C10.3. The results are as follows:

- The alternative sources of HRQL data from the systematic literature review have negligible impact on results.
- Factoring in the reduced treatment effect following neutralising antibody formation associated with ERT has negligible impact on the results, probably because of the low individual annual risk of developing antibodies.
- Starting the cohort simulation at the younger age results in higher QALYs, life years and costs compared to the base case, as expected. There is a greater difference between migalastat and ERT observed in the 16-year-old cohort than the base case. This is due to higher discontinuation of ERT over the extended patient follow-up.
- Factoring in the cost impact of infusions on patients and caregivers in the analysis of the societal perspective results in slightly lower incremental costs (1%). Note that the disutility of the disease and infusions on caregivers has not been explicely captured in the model thus is likely to underestimate the quality of life benefit of migalastat.
- Applying reduced rates of disease progression in line with observations for the composite endpoint in ATTRACT results in improvements in QALYs (26%) and a slight increase in costs (5%).
- Reducing the time horizon from a lifetime to 20 years results in both lower costs and lower QALYs, as expected.
- Using alternative disutilities relating to infusions from the DCE results in incremental QALYs of up to 2.23. In this scenario, disutilities for all attributes surveyed (mode of administration, infusion reactions, headaches (both ERT and migalastat) and antibodies) were included in the analysis, which reflects the high preference for a convenient, more tolerable oral regimen over an infusion.
- Assuming an equal market share between agalsidase alfa and agalsidase beta results in a small increase in costs (3%).

Table D12.34: Scenario analysis results

	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)	1,268,674	-	0.98	0%
Utilities scenario 2: Gold et al (2002)	1,268,674	-	0.98	0%
Reduced efficiacy 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%

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Mean probabilistic sensitivity analysis results are presented in Table D12.35. Histograms illustrating the distribution of the results of the 1,000 simulations are illustrated in Figures D12.8 and Figure D12.9.

Table D12.35: Probabilistic sensitivity analysis results

	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

Figure D12.8: Histogram of probabilistic sensitivity analysis cost results

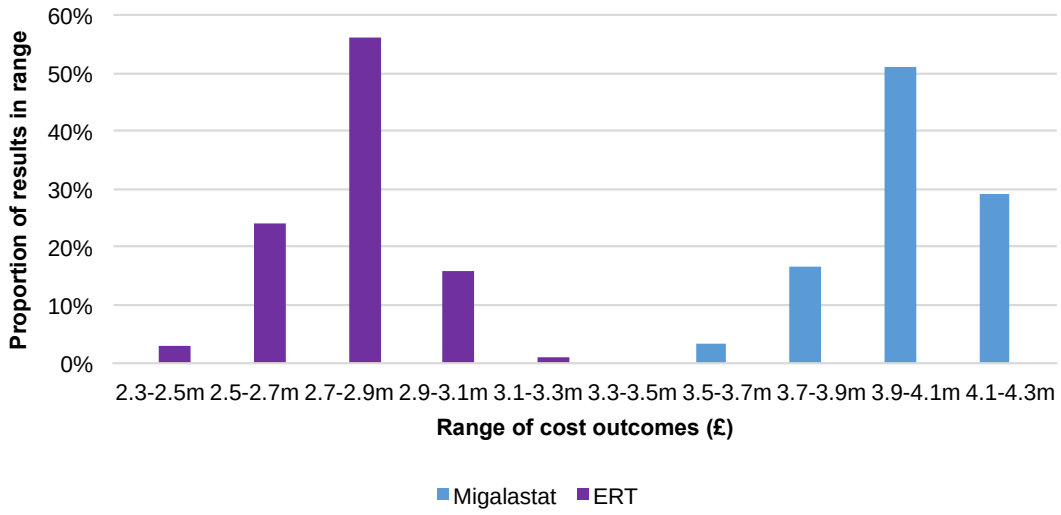
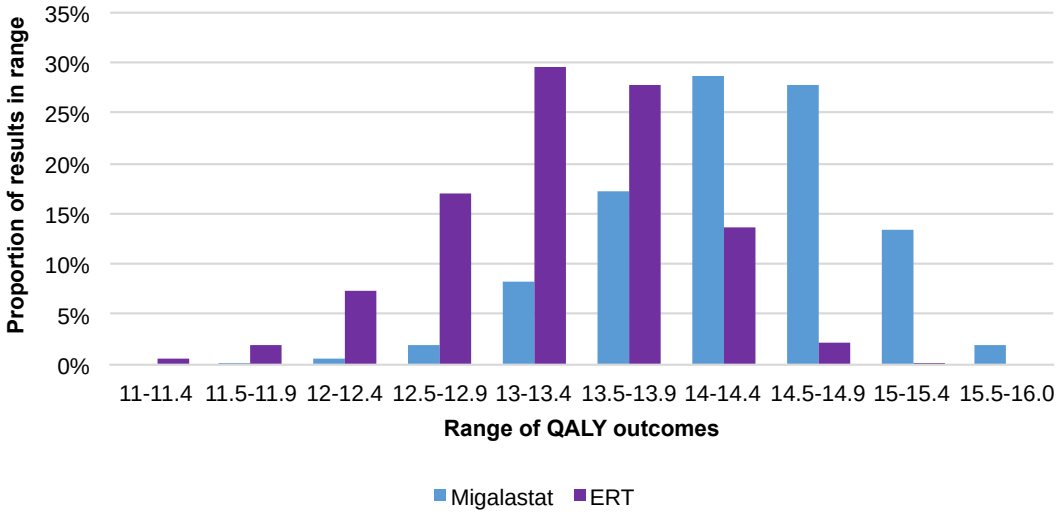


Figure D12.9: Histogram of probabilistic sensitivity analysis QALY results



12.5.14 What were the main findings of each of the sensitivity analyses?

Results are most sensitive to variations in discount rates, gender distribution, disutilities relating to infusions and transition probabilities. The results are also sensitive to the baseline charactertics of the cohort (age and health state distribution) and time horizon. The most influential parameter on cost results is the annual price of migalastat, followed by the discontinuation rate. The market shares of agalsidase alfa and agalsidase beta also impact the difference in costs.

12.5.15 What are the key drivers of the cost results?

The cost results are predominantly driven by treatment cost, followed by administration costs. Migalastat and ERT are assumed to be equally effective and although there are slight differences in probability of experiencing an adverse event, the costs are negligible compared with the treatment costs.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

Subgroup analysis was not conducted as it is not in the scope.

12.6.2 Define the characteristics of patients in the subgroup(s).

Subgroup analysis was not conducted as it is not in the scope.

12.6.3 Describe how the subgroups were included in the cost-consequence analysis.

Subgroup analysis was not conducted as it is not in the scope.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis).

Subgroup analysis was not conducted as it is not in the scope.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Subgroup analysis was not conducted as it is not in the scope.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

To model has been validated by internal and external health economists to ensure it is technically accurate. The model design and construct has been ratified by clinical experts to ensure the assumptions are valid and the model reflects clinical practice.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-consequence analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

It is difficult to compare the results of this analysis with that of Rombach et al given the differences in population characteristics and the lack of a “no treatment” comparator.

Connock et al (2006) assumed a ‘perfect drug’ scenario that is not reflective of clinical practice so a comparison is not possible.

Moore et al (2007) did not present total cost, QALY and life year results by cost type and therefore a comparison is not possible.

12.8.2 Is the cost-consequence analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

This analysis is relevant to the entire Fabry population eligible for migalastat in England.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

This model presents a number of strengths. Its structure was based on a previously peer-reviewed, published model and was validated with experts. Although the transition probabilities were estimated in a Dutch cohort of patients with Fabry disease, efforts were made to collect input data that were UK-specific or representative of UK patients with Fabry disease. The analysis also adopted a conservative approach, assuming migalastat and ERT had similar efficacy. The ATTRACT trial of migalastat compared to ERT showed trends towards some benefit of migalastat in terms of change in clinical biomarkers such as eGFR, LVMI and α-Gal A activity. It is possible that these improvements would be translated into clinical benefits over longer follow-up. However, in order to be conservative the model did not account for this potential benefit.

This analysis also presents some limitations. The rarity of Fabry disease means that patient numbers were low, therefore, the variability was high. For example, a 10% cut-off for selecting AEs in the clinical trial was used; in some cases, this amounts to two patients in the study.

The model was adapted from Rombach et al (2013a) and therefore inherited some of their limitations too. Notably, low patient numbers in the registry the authors used to estimate their transition probabilities did not allow to differentiate transitions from 2 or 3 complications to death. Also, their analysis for untreated patients relied on the period prior to the introduction of ERT; while their analysis for treated patients relied on the period since the introduction of ERT. The two periods differ in the diagnosis and management of Fabry disease, as well as the availability of treatments and are, therefore, not directly comparable.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further research is needed to improve this model. The extension study of ATTRACT should allow long-term collection of outcome data with migalastat, while there exists two registries of patients with Fabry disease in Europe that include more than five years of data for patients on ERT already. These sources combined should allow more robust estimates of patient progression while being treated, as well as more insight into clinical outcomes that the model could not capture such as gastrointestinal symptoms and depression.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

A prevalence rate for Fabry disease with signs and symptoms is applied to the general population of England (Office for National Statistics, 2015c) to estimate the number of patients with Fabry disease with signs and symptoms. The prevalence rate was obtained from a report by the Northern Genetics Service in the North of England (Brennan and Parkes, 2014), which estimated prevalence of symptomatic Fabry disease to be 1 in 64,600 (0.002%). Although estimated for Northern England, the authors indicated that this estimate is representative of the UK population.

In the absence of a diagnosis rate for England in the published literature, it is assumed that the UK rate calculated from the Fabry registries can also be applied to England. The diagnosis rate for the UK is derived using the prevalence of Fabry disease with signs and symptoms and the recorded diagnoses in the UK, based on the number of patients enrolled in the Fabry Disease Registry (Fabry Disease Registry, 2015) and Fabry Outcome Survey (Fabry Outcome Survey, 2015). These sources represent the most reliable records of diagnosed patients in the UK. There were 418 patients enrolled in the Fabry Disease Registry in 2015 and 436 enrolled in the Fabry Outcome Survey in 2015, totalling 854 diagnosed UK patients. Patients may be enrolled in both registries so a 10% overlap of patients is assumed. To account for patients who are diagnosed but not in the databases, a 3% gross-up is applied.

The diagnosis rate is calculated as the proportion of recorded diagnosed patients (792) compared to the theoretical number of prevalent UK patients (1,008) and is assumed to be constant. This constant diagnosis rate of 78.6% is applied to the prevalence estimate for England in 2016 to estimate the number of patients diagnosed with Fabry disease (Table D13.1).

Based on analyses of Fabry Disease Registry patient records (Fabry Disease Registry, 2015), 60% of these diagnosed patients with signs and symptoms are being treated with ERTs in the UK.

Migalastat eligibility criteria includes patients who have mutations amenable to migalstat's mechanism of action, are 16 years or older, and are not diagnosed with ESRD. To determine the number of patients eligible for migalastat, estimated proportions are applied to the diagnosed, treated patients with Fabry disease (Table D13.1), as follows:

- 30%-50% of treated patients have amenable mutations (midpoint of 40% used in base case) (Benjamin et al., 2009; Filoni et al., 2010; Germain et al., 2012; Shabbeer et al., 2006; Ishii et al., 2007; Wu et al., 2011).

- 97% of treated patients are 16+: obtained from a longitudinal cohort study of people with lysosomal storage disorders in the UK for the National Institute for Health Research (NIHR) (Wyatt et al., 2012), which reported that approximately 3% of patients with symptomatic Fabry disease were under age 16.
- 91% of treated patients do not have ESRD: average of a reported 83% for males and 99% for females, obtained from an analysis of UK Fabry Registry data (Mehta et al., 2004).

Table D13.1: Derivation of number of diagnosed patients on treatment in the first year

Population of England in 2016	55,218,701	
Prevalence of Fabry disease with signs/symptoms	0.002%	855
Proportion of patients diagnosed with signs/symptoms	78.6%	672
Proportion of diagnosed patients receiving treatment	60%	403
Proportion of treated patients with amenable mutations	40%	161
Proportion of treated patients aged 16+	97%	156
Proportion of treated patients without ESRD	91%	142
Number of diagnosed patients eligible for migalastat	142	

Table D13.2 shows the number of patients that will be eligible for treatment with migalastat in the next five years according to the population projections for England (based on calculations from Table D13.1).

Table D13.2: Derivation of number of patients eligible for treatment with migalastat in the subsequent 5 years

	Year 1	Year 2	Year 3	Year 4	Year 5
Projected population of England (2017 to 2021)	55,640,415	56,061,460	56,466,327	56,862,331	57,248,364
Number of expected diagnosed patients eligible for migalastat	143	145	146	147	148

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

The future market shares are estimated based on previous market research studies and anticipated uptake of migalastat in the market. Distinct market share distributions are assigned to prevalent and incident treated patients.

It is assumed that some percent of eligible prevalent patients are likely to switch to migalastat from ERT and the migalastat uptake will gradually increase following its availability to reflect

its adoption by physicians. The impact of migalastat on ERT shares is assumed to be proportional to the current clinical expert estimated market shares of ERT (70% agalsidase alfa, 30% agalsidase beta). The market shares for migalastat are presented in Table D13.3 and the resulting patient numbers for each intervention are provided in Table D13.4. Potential discontinuations from migalastat or treatment switches are not modelled explicitly, however they are implicitly accounted for via overall market shares for ERT and migalastat over time.

Table D13.3: Market shares in eligible patient population for migalastat

	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]

Table D13.4: Patient counts in eligible population for revised market with migalastat

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent treated patients					
Migalastat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**143**	**145**	**146**	**147**	**148**
Incident treated patients					
Migalastat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**1**	**1**	**1**	**1**	**1**
Total treated population					
Migalastat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**145**	**146**	**147**	**148**	**149**

Note: All figures calculated. Some totals may appear to sum incorrectly due to rounding.

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Since migalastat is an oral medication, there are no associated administration, or specific temperature-controlled storage or transport/delivery, costs.

No extra tests are required to determine those patients who have amenable mutations as standard genetic testing for Fabry disease can identify the mutation, which is then compared with a database of all know mutations developed by Amicus Therapeutics. Where the mutation is unknown, Amicus Therapeutics cover the cost of any extra testing required.

13.4 Describe any estimates of resource savings associated with the use of the technology.

ERT is administered through bi-weekly infusions. A weighted average administration cost per infusion for each ERT is calculated by considering the proportion of infusions that are nurse-administered. In England, based on inputs from clinical experts, 100% of the ERT-treated patients are on homecare, of which 50% use a homecare nurse. The cost for nurse-administered home infusions is estimated as the cost of each nurse visit plus a £200 delivery charge and then multiplied by 26 to estimate the annual cost of administration. Nurse visit costs for agalsidase alfa and agalsidase beta are approximated using the clinical nurse specialist cost of £91 per hour (patient contact time) provided in the PSSRU (Curtis and Burns, 2015).

As per the cost-consequence analysis, the following nurse costs are applied:

- For agalsidase beta, 2-hour infusion + 45 minutes for preparation/clean-up = £250.
- For agalsidase alfa, 40-minute infusion + 45 minutes for preparation/clean-up = £129.

A one-time annual nurse visit is also required for self-administered home infusions for training purposes. Table D13.5 shows the weighted average administration cost per home infusion, which also includes pre-medical costs as defined in Section 12.3.6.

Table D13.5: Administration costs of ERT

	Agalsidase beta		**Agalsidase alfa**	
Infusion cost				
Cost of homecare	£200		£200	
Cost of nurse visit	£250		£129	
Location of infusion				
Home	100%		100%	
Administration	Self	Nurse	Self	Nurse
	50%	50%	50%	50%
Nurse visits per year	1	26	1	26
Pre-medication per infusion	£0.26		£0.26	
Weighted annual cost	**£8,581.76**		**£6,948.26**	

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Migalastat is not associated with the infusion-associated reactions (IARs) that commonly occur with ERT because it is an oral agent. There is therefore no requirement for post-infusion medications that are used to alleviate infusion-related side effects, which represents a saving to the NHS. Further to the reduction in administration costs, the time that would have been spent by a homecare nurse visiting the patient in order to administer ERT is recovered.

ERTs are administered based on patient weight, which varies by individual patients and is therefore a parameter that the budget impact is sensitive to. Migalastat will reduce this uncertainty as it is not associated with a weight-based dosing.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

The time required for an ERT infusion can be far longer than noted in the product labelling. If an IAR occurs, it usually means that the infusion must be interrupted or the infusion rate slowed, prolonging the infusion time. The pre-medication required for ERT can incapacitate patients for the whole day or longer, interfering with school, work, and family responsibilities.

By removing the need for bi-weekly transfusions, patients with Fabry disease with amenable mutations may remain productive members of society; one to two days every fortnight will not be lost because of infusions. Therefore, adult patients and caregivers can remain at work, and adolescent patients can remain at school or college, so that their contributions to society are not lessened.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Since ERT is subject to tender, the exact price paid is unknown. The base case assumes an ERT discount rate of 3%.

The Health Survey for England 2014 provides the average weight for males (84 kg) and for females (71.1 kg). Using clinical expert opinion that 50% of symptomatic patients with Fabry disease are male, the average weight is then 77.6 kg. Scenario analysis is conducted using the mean weight from ATTRACT (74.1 kg).

The following tables show the cost for both the current and revised market scenarios with the budget impact estimated to be the difference. Results are presented per year, disaggregated by cost categories (e.g. acquisition and administration costs) in Table D13.6.

Table D13.6: Base case budget impact disaggregated by cost categories

	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]

The budget impact analyses conducted suggest that the introduction of migalastat for the management of patients with amenable mutations at the list price will lead to an increase in the overall budget associated with the management of Fabry disease in England. The main driver of the increase in the overall budget is estimated to be the acquisition of migalastat, which is more costly than ERT. There is reduced uncertainty surrounding budget impact via removing the need for weight-based dosing. Substantial savings of up to [redacted] per year will be made with migalastat through the elimination of infusions of ERT. Finally, although it has not been considered in this model, the elimination of infusions due to migalastat's innovative mode of administration would remove the need for post-infusion medications that are used to alleviate infusion-related reactions and address the potential impact of infusions on the patient's productivity and quality of life.

Sensitivity analysis

Since ERT is subject to tender, the exact price paid is unknown. The base case assumes an ERT discount rate of 3%. Scenario analyses with this rate varied from 0% to 7% demonstrate the impact on budget impact per year (Table D13.7).

Table D13.7: Sensitivity analysis on ERT discount rate

ERT discount	Year 1	Year 2	Year 3	Year 4	Year 5
0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case: 3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The effect of patient weight on costs is also explored in a scenario in which the mean weight from ATTRACT (74.1 kg) is used rather than the general population weight (77.6kg) (Table D13.8). A 3.5 kg reduction in average patient weight results in an increased budget impact by up to 3.4% per year.

It has been estimated that 30%-50% of treated patients would have amenable mutations and thus a midpoint of 40% was used in the base case analysis (Benjamin et al., 2009; Filoni et al., 2010; Germain et al., 2012; Shabbeer et al., 2006; Ishii et al., 2007; Wu et al., 2011). The budget impact results are sensitive to scenarios exploring 30% and 50% amenable mutations.

Assuming an equal market share of agalsidase beta and agalsidase alfa has a relatively minor impact on the base case, which assumes a 70% market share for agalsidase alfa.

Table D13.8: Sensitivity analysis on budget impact

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean 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]

Overall, introduction of migalastat at the list price is anticipated to increase the overall budget impact for the management of patients with Fabry disease. However, migalastat will replace existing options, rather than increasing the overall market size or adding on to existing therapies, for a well-defined patient group which will limit the budget increase within the health system.

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

There is uncertainty around the cost of ERT in the model:

- The cost of a nurse administering an infusion of ERT at home is based on the cost of a clinical nurse specialist from PSSRU.
- Since ERT dosage is based on weight, the cost of ERT acquisition is sensitive to the average weight used.
- Since ERT is subject to tender, the exact price paid is unknown.

Due to lack of published, data-driven estimates on the incidence of Fabry disease in the UK (or sufficient surrogates), the model employs methodological assumptions to estimate the annual incident population. It is assumed that the introduction of migalastat will not drastically increase the size of the patient population eligible for therapies, based on the treatment guidelines (Hughes and Ramaswami, 2005) which suggest patients who can be considered for migalastat are already considered for ERT. The base-case assumes that incidence is driven by population growth. While the prevalence, diagnosis, and treatment rates remain

constant throughout the time horizon, the UK population grows annually and as a result so does the Fabry disease patient population. The new patients that appear each year are assumed to be incident patients. All-cause mortality is not modelled explicitly in the model due to the short time horizon of the analysis.

Section E – Impact of the technology beyond direct health benefits and on the delivery of the specialised service

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

Section 15 is aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

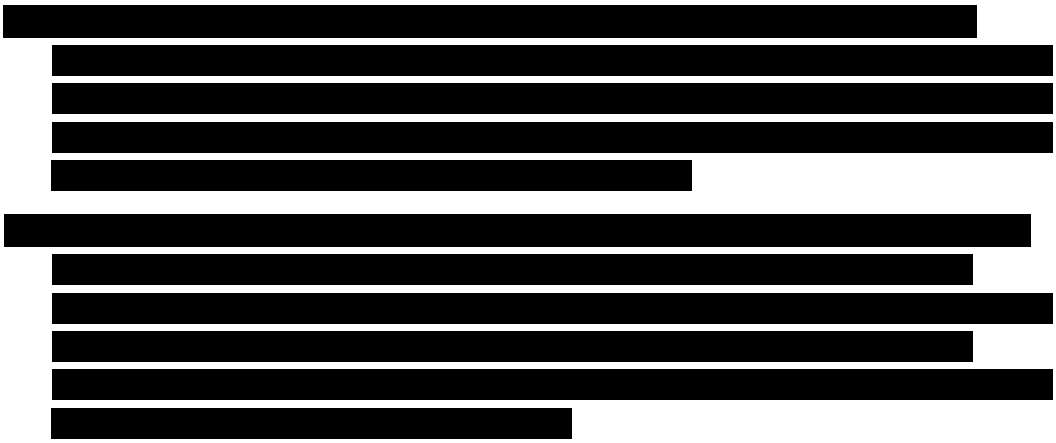
14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

A proportion of the benefit and cost savings relating to migalastat will be incurred outside of the NHS.

Based on the evidence that is currently available, migalastat is comparable to ERT in terms of slowing the progression of disease, and may have additional clinical benefits such as improving cardiac function. As discussed in Section 7, Fabry disease can affect all aspects of daily life and can lead to issues in social interactions, school attendance, sports participation, and employment opportunities (Sivley, 2013; Laney et al., 2010). Deficits in social functioning such as reduced participation in school, sports, social activities, and employment have been found in both male and female patients with Fabry disease (MacDermot et al., 2001b, 2001a; Laney et al., 2010). In a study performed before ERT became available, based on 98 men in the UK Fabry disease registry, just over half were employed, even though most patients were in their thirties (MacDermot et al., 2001b). In another study including males and females in which the majority of patients (65%, N=184, mean age 44 years) were receiving ERT, 59%

were employed (Cole et al., 2007). In this study, approximately 16% noted that they were unemployed due to sickness or disability, which was significantly higher than in the national population (4%). A further recent study found no significant difference in employment rates between young adults with Fabry disease (median age 25 for males and 27 for females), most of whom were being treated with ERT, and a matched control group (71% vs. 76% employed, respectively) (Bouwman et al., 2011). Although difficult to compare the results of these studies, this suggests that the availability of ERT has improved employment rates for patients with Fabry disease. Provision of a further effective treatment option is expected to help patients stay in employment for longer and offset costs due to loss of employment or reduction in working days.

Migalastat has the additional benefit over current therapies as it is an oral therapy and will not interrupt working life as infusions can do. As described in Section 7, the Fabry Infusion Survey illustrated that ERT can incapacitate patients for a whole day or longer, interfering with school, work, and family responsibilities (n=80):



In the UK Fabry Disease Patient Survey (2016), described in Section 7, patients also reported having to take time off work to have their infusion (several patients had already had to give up work or work part-time due to their Fabry disease).

As an oral treatment, migalastat offers a more convenient alternative to ERT that will avoid loss of productivity from ERT infusions, as well as avoiding IARs and development of neutralising antibodies (Parini et al., 2010). This was reflected in the UK Fabry Disease Patient Survey (2016), where two patients being treated with migalastat confirmed that it is convenient and far less restrictive than ERT “it has made life so much easier and I can’t think of anything negative to say about it”.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It is difficult to quantify savings to other government bodies and these would not be anticipated to be different from savings incurred through current therapy. In the long-term, stabilising disease progression of patients with Fabry will reduce serious complications and the resultant incapacitation. The more independent and capable the patient is, the less dependent they – or their caregivers - are on respite care, or on disability and other welfare payments.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Costs borne by patients/ caregivers include out of pocket expenses, such as travel expenses for clinic visits. Patients may have loss of earnings as a result of their illness or due to their infusions.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

The impact of Fabry disease goes far beyond the impact on the patient. Family members and other informal caregivers are involved in the care of patients as well as the management of their disease and, as discussed in Section 7, experience stress and fatigue as a result of caregiving responsibilities (Street et al., 2006).

There are limited published data on the time spent by family members or other caregivers in providing care to Fabry patients, however caring for a patient with long-term complications such as renal failure, would be expected to present a significant burden. In a study that evaluated burden of chronic dialysis patients on family caregivers in Spain, the HRQL of caregivers was worse than that of age and gender-matched populations. Younger family members, who were the primary carers of older dialysis patients with poor HRQL, experienced a higher burden, had a worse HRQL and had a higher risk of clinical depression (Alvarez-Ude et al., 2004).

In addition, time taken by caregivers to assist or supervise infusions may be significant and would be saved if replaced by an oral therapy. In the UK Fabry Infusion Survey described in Section 7 the average infusion time for patients on bi-weekly ERT was [redacted] (Amicus Therapeutics, 2015e).

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The safety and efficacy of migalastat has been studied in a robust clinical study programme. 168 patients received migalastat in phase 2 and phase 3 trials, 119 have been treated for >1 year and one patient has been treated for 9 years with no drug-related AEs observed (Schiffmann et al., 2015b; Amicus Therapeutics, 2015b). The phase 3 studies for migalastat included 127 patients with Fabry and have provided valuable and robust evidence relating to the efficacy of migalastat versus the current standard of care (ERT) as well as compared to untreated patients. The efficacy of migalastat was demonstrated based on endpoints that are relevant to both patients and the clinicians monitoring their care. This included short-term outcomes such as gastrointestinal events, as well as renal and cardiac function and rates of renal, cardiovascular, and cerebrovascular events.

Amicus Therapeutics sponsored an international survey of people living with Fabry disease and parent/guardians of those under age 18, which has provided a better understanding of the burden of treatment with the existing ERTs and the effect on these patients' lives. Results from this survey revealed that ERT use was associated with significant burdens on patients with Fabry disease (see Section 7).

Amicus Therapeutics has also commissioned a study to explore the value that is placed on improvements to the treatments for Fabry disease. The study incorporated a discrete choice experiment which provides valuable information about the relative importance of different Fabry treatment attributes (described in Section 10.1.9).

The open-label extension study AT1001-042 is ongoing and is collecting long-term safety and efficacy data including changes in eGFR and LVMi and HRQL. In addition, Amicus are currently allowing access to migalastat following physician-initiated request, for specific patients with Fabry disease who do not meet requirements for participation in an existing migalastat clinical study (Canada and Australia only). Safety data will be collected from this study (AT1001-188).

14.6 Describe the anticipated impact of the technology on innovation in the UK.

UKTI's managing director in their annual report for 2015 said "It is crucial for the long term retention of the UK's position as the leading destination for FDI (Foreign Direct Investments) into Europe that we broaden the global base from which foreign investments are generated" (UKTI, 2015). Amicus Therapeutics is a good example of such direct investment. Further to this, UKTI Life Sciences Investment Organisation's (LSIO) chief executive Mark Treherne has regularly stated that inbound companies act as a catalyst for further clinical research and innovation. Based on the highly innovative nature of Amicus' technology, being at the forefront of chaperone technology for rare and orphan diseases, Amicus is an ideal example of the type of company and innovative approach that the UKTI and LSIO are trying to attract to the UK.

Birmingham, Cambridge, London and Manchester are all designated national centres for the diagnosis and management of LSDs, and have extensive experience of treating patients with Fabry disease. Four centres in the UK participated in the clinical studies for migalastat (Hope Hospital, Salford; the Royal Free Hospital, London; Addenbrooke's Hospital, Cambridge; and National Hospital for Neurology and Neurosurgery, London). The addition of chaperone therapy for Fabry Disease is a novel therapeutic approach and mode of action when compared with more traditional enzyme replacement therapies, will act as a catalyst for new clinical research and trials for associated technologies.

Gaining further experience with migalastat in clinical practice will advance clinical knowledge and strengthen the UK-reputation as a centre for world-leading research in lysosomal storage disorders. Providing access to treatments for rare diseases will encourage wider research initiatives and clinical trial programmes in the UK as well as investment in the UK pharmaceutical industry.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

There are currently two patient registries that include patients that have been treated with ERT:

- FOS – the Fabry Outcome Survey (sponsored by Shire) – was initiated in 2001 to gain further understanding of the nature of Fabry disease and to improve the clinical management of patients with this disorder. FOS is an outcomes database for all patients with Fabry disease, including women and children, who are receiving, or are candidates for, enzyme replacement therapy (ERT) with agalsidase alfa
- The Fabry Registry (sponsored by Genzyme) is an ongoing, observational database that tracks the natural history and outcomes of patients with Fabry disease. All Fabry disease patients are eligible for enrolment irrespective of their treatment status, and all physicians managing patients with Fabry disease are encouraged to participate in the Fabry Registry.

There is some overlap between the databases as some patients are enrolled in both.

Amicus intend to work with the EMA and clinicians to ensure that any monitoring requirements are honoured whilst minimising any reporting and logistical burden on clinicians and patients.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Based on discussions with clinical experts, it was felt that similar criteria for review of effectiveness that currently exist for ERT would be appropriate with 6 and 12 monthly monitoring as per the English SOP on the management of Fabry (Amicus Therapeutics, 2016a; Hughes et al., 2013a).

15 Impact of the technology on delivery of the specialised service

15.1 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The draft Summary of Product Characteristics for migalastat states that treatment with migalastat should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease. In England, it is expected that initiation of therapy will occur only at designated specialist LSD centres. Patients would continue to be monitored

on a regular basis at one of the specialist LSD centres, according to current clinical practice. It is advised to periodically monitor renal function, echocardiographic parameters and biochemical markers (every 6 months) in patients initiated on or switched to migalastat (Amicus Therapeutics, 2016c). This is in line with current NHS England's SOP and practice regarding the monitoring of patients on ERT, therefore no additional monitoring is required with migalastat. It is expected that dispensing of migalastat would transition to homecare arrangements as per existing ERT.

15.2 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No additional infrastructure is anticipated. Migalastat is an oral therapy and will be prescribed and monitored within existing services for LSDs and will offer an additional treatment option for genetically amenable Fabry disease patients.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

The following section describes a single systematic search of the literature that was conducted to identify studies of interest reporting **clinical efficacy, safety, HRQL, and economic evidence**. Searches were conducted in the following databases to identify literature published from database inception to present (December 2015):

- MEDLINE (via PubMed)
- Embase
- The Cochrane National Health Service Economic Evaluation Database (NHS EED)
- The Cochrane Health Technology Assessment (HTA) Database
- The Database of Abstracts of Reviews of Effects (DARE)[4]
- EconLit

17.1.2 The date on which the search was conducted.

The published literature searches were conducted on 07 December 2015.

The searches of clinical trials registers and conference proceedings were conducted on 08 December 2015.

17.1.3 The date span of the search.

There was no publication date limit applied for the published literature database searches. Information from clinical trials registers and conference proceedings was limited to the last

[4] National Institute for Health Research (NIHR) funding to produce DARE and NHS EED ceased at the end of March 2015; however, both databases can still be accessed via the Centre for Reviews and Dissemination (CRD) website. Searches of MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsychInfo and PubMed were continued until the end of 2014. Bibliographic records were published on DARE and NHS EED until 31st March 2015. The HTA database will continue to be produced by CRD for the foreseeable future.

three years (2013-2015). Publications identified from the manual checking of reference lists of relevant systematic literature reviews was limited to the past year (2015).

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategies for each database are presented below:

MEDLINE

Domain		**MEDLINE Search Algorithm**
Population	#1.	Fabry[tiab]
Economic	#2.	cost*[TIAB] OR “economic”[TIAB] OR budget*[TIAB] OR “expenditure”[TIAB] OR (“resource”[TIAB] AND “utilization”[TIAB]) OR (“resource”[TIAB] AND “utilisation”[TIAB]) OR (“resource”[TIAB] AND “use”[TIAB]) OR (“health”[TIAB] AND “care”[TIAB] AND “utilization”[TIAB]) OR (“health”[TIAB] AND “care”[TIAB] AND “utilisation”[TIAB]) OR (“health”[TIAB] AND “care”[TIAB] AND “use”[TIAB]) OR (“healthcare”[TIAB] AND “utilization”[TIAB]) OR (“healthcare”[TIAB] AND “utilisation”[TIAB]) OR (“healthcare”[TIAB] AND “use”[TIAB]) OR “economic evaluation”[TIAB] OR “cost benefit”[TIAB] OR “cost effectiveness”[TIAB] OR “cost utility”[TIAB] OR “cost minimization”[TIAB] OR “cost minimisation”[TIAB] OR “cost savings”[TIAB] OR “cost saving”[TIAB] OR “pharmaceutical economics”[TIAB] OR “budget impact”[TIAB] OR “econometric”[TIAB] OR “markov”[TIAB] OR “decision analysis”[TIAB] OR “discrete event simulation”[TIAB] OR (“model”[TIAB] OR “models”[TIAB] OR “modeling”[TIAB] OR “modelling”[TIAB] AND (cost*[TIAB] OR “economic”[TIAB] OR “economics”[TIAB])) OR "work loss"[TIAB] OR productivity[TIAB] "indirect cost"[TIAB] OR fee[tiab] OR fees[tiab] OR budget*[tiab] OR expenditure*[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR "resource use"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR employment[tiab] OR retirement[tiab] OR absenteeism[tiab] OR presenteeism[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR "caregiver burden"[tiab] OR hospital*[tiab] OR “emergency room visit”[tiab] OR “emergency room visits”[tiab] OR “ER visit” [tiab] OR “ER visits” [tiab] OR “emergency department visit”[tiab] or “emergency department visits”[tiab] OR “ED visit” [tiab] OR “ED visits”[tiab] OR inpatient*[tiab] OR outpatient*[tiab]
	#3.	#1 AND #2
Humanistic	#4.	QALY[TIAB] OR QALYs[TIAB] OR "Quality-Adjusted Life Years"[TIAB] OR “quality adjusted life year”[TIAB] OR “quality adjusted life years”[TIAB] OR “quality of life”[TIAB] OR "quality-of-life" [TIAB] OR (utilit*[TIAB] AND “health”[TIAB]) OR (utilit*[TIAB] AND scor*[TIAB]) OR (utilit*[TIAB] AND valu*[TIAB]) OR (disutilit*[TIAB] AND “health”[TIAB]) OR (disutilit*[TIAB] AND scor*[TIAB]) OR (disutilit*[TIAB] AND valu*[TIAB]) OR “DALY”[TIAB] OR “DALYs”[TIAB] OR “disability adjusted life year”[TIAB] OR “disability adjusted life years”[TIAB] OR “sf 36”[TIAB] OR “short form 36”[TIAB]

		OR “EQ 5D”[TIAB] OR “EuroQOL 5D”[TIAB] OR PedsQL[tiab] OR FPHPQ[tiab] OR AFD[tiab] OR “pain questionnaire”[tiab] OR BPI[tiab] OR “brief pain inventory”[tiab] OR FPQ[tiab]
	#5.	#1 AND #4
Clinical efficacy and safety	#6.	"randomized controlled trial"[tiab] OR "randomised controlled trial"[tiab] OR randomi*[tiab] OR RCT[tiab] OR "controlled trial"[tiab] OR single-blind*[tiab] OR double-blind*[tiab] OR placebo[tiab] OR crossover[tiab] OR open-label[tiab] OR "observational cohort"[tiab] OR safety[tiab] OR efficacy[tiab] OR "comparative effectiveness"[tiab] OR tolerability[tiab] OR "adverse event"[tiab]
	#7.	#1 AND #6
BOI	#8.	#3 OR #5 OR #7
Filter	#9.	Humans
Primary studies	#10.	"Case Reports" [Publication Type] OR "Letter" [Publication Type] OR "Editorial" [Publication Type]
	#11.	#9 NOT #10
	#12.	Review[Publication Type] NOT (systematic OR meta AND analy* OR (indirect OR mixed AND "treatment comparison"))
Studies to be evaluated in the SLR	#13.	#11 NOT #12

EMBASE

Domain		**Embase Search Algorithm**
Population	#1.	Fabry:ab,ti
Economic	#2.	cost*:ab,ti OR ‘economic’:ab,ti OR budget*:ab,ti OR ‘expenditure’:ab,ti OR (‘resource’:ab,ti AND ‘utilization’:ab,ti) OR (‘resource’:ab,ti AND ‘utilisation’:ab,ti) OR (‘resource’:ab,ti AND ‘use’:ab,ti) OR (‘health’:ab,ti AND ‘care’:ab,ti AND ‘utilization’:ab,ti) OR (‘health’:ab,ti AND ‘care’:ab,ti AND ‘utilisation’:ab,ti) OR (‘health’:ab,ti AND ‘care’:ab,ti AND ‘use’:ab,ti) OR (‘healthcare’:ab,ti AND ‘utilization’:ab,ti) OR (‘healthcare’:ab,ti AND ‘utilisation’:ab,ti) OR (‘healthcare’:ab,ti AND ‘use’:ab,ti) OR ‘economic evaluation’:ab,ti OR ‘cost benefit’:ab,ti OR ‘cost effectiveness’:ab,ti OR ‘cost utility’:ab,ti OR ‘cost minimization’:ab,ti OR ‘cost minimisation’:ab,ti OR ‘cost savings’:ab,ti OR ‘cost saving’:ab,ti OR ‘pharmaceutical economics’:ab,ti OR ‘budget impact’:ab,ti OR ‘econometric’:ab,ti OR ‘markov’:ab,ti OR ‘decision analysis’:ab,ti OR ‘discrete event simulation’:ab,ti OR (‘model’:ab,ti OR ‘models’:ab,ti OR ‘modeling’:ab,ti OR ‘modelling’:ab,ti AND (cost*:ab,ti OR ‘economic’:ab,ti OR ‘economics’:ab,ti)) OR ‘work loss’:ab,ti OR productivity:ab,ti ‘indirect cost’:ab,ti OR fee:ab,ti OR fees:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR ‘resource utilization’:ab,ti OR ‘resource utilisation’:ab,ti OR ‘resource use’:ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR employment:ab,ti OR retirement:ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR ‘sick leave’:ab,ti OR ‘sick day’:ab,ti OR ‘caregiver burden’:ab,ti OR hospital*:ab,ti OR 'emergency room visit':ab,ti OR 'emergency room visits':ab,ti OR 'er visit':ab,ti OR 'er visits':ab,ti OR 'emergency department visit':ab,ti OR 'emergency department visits':ab,ti OR 'ed

		visit':ab,ti OR 'ed visits':ab,ti OR inpatient*:ab,ti OR outpatient*:ab,ti
	#3.	#1 AND #2
Humanistic	#4.	QALY:ab,ti OR QALYs:ab,ti OR 'Quality-Adjusted Life Years':ab,ti OR 'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR 'quality of life':ab,ti OR 'quality-of-life':ab,ti OR (utilit*:ab,ti AND 'health':ab,ti) OR (utilit*:ab,ti AND scor*:ab,ti) OR (utilit*:ab,ti AND valu*:ab,ti) OR (disutilit*:ab,ti AND 'health':ab,ti) OR (disutilit*:ab,ti AND scor*:ab,ti) OR (disutilit*:ab,ti AND valu*:ab,ti) OR 'DALY':ab,ti OR 'DALYs':ab,ti OR 'disability adjusted life year':ab,ti OR 'disability adjusted life years':ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'EQ 5D':ab,ti OR 'EuroQOL 5D':ab,ti OR PedsQ:ab,ti OR FPHPQ:ab,ti OR AFD:ab,ti OR 'pain questionnaire':ab,ti OR BPI:ab,ti OR 'brief pain inventory':ab,ti OR FPQ:ab,ti
	#5.	#1 AND #4
Clinical efficacy and safety	#6.	'randomized controlled trial':ab,ti OR 'randomised controlled trial':ab,ti OR randomi*:ab,ti OR RCT:ab,ti OR 'controlled trial':ab,ti OR single-blind:ab,ti OR single-blinded:ab,ti OR double-blind:ab,ti OR double-blinded:ab,ti OR placebo:ab,ti OR crossover:ab,ti OR open-label:ab,ti OR 'observational cohort':ab,ti OR safety:ab,ti OR efficacy:ab,ti OR 'comparative effectiveness':ab,ti OR tolerability:ab,ti OR 'adverse event':ab,ti
	#7.	#1 AND #6
BOI	#8.	#3 OR #5 OR #7
Filter	#9.	Humans
Primary studies	#10.	[editorial]/lim OR [letter]/lim OR [note]/lim
	#11.	#9 NOT #10
	#12.	[Review]/lim NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison'))
Studies to be evaluated in the SLR	#13.	#11 NOT #12

COCHRANE (DARE, NHS EED and HTA Databases) and EconLit

Domain		**Cochrane Search Algorithm**
Population	#1.	Fabry (title, abstract, keywords)

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Supplementary searches of “grey” literature were performed to complement the literature database searches and provide data from recent or ongoing trials. Sources for these searches included:

- Registers of clinical trials: clinicaltrials.gov, clinicaltrialsregister.eu, the United States (US) Food and Drug Administration (FDA) website, European Medicines Agency (EMA) website, National Institute for Health and Care Excellence (NICE) website, United Kingdom Society for Mucopolysaccharide Diseases (UK MPS) website, and websites of manufacturers of comparator products for migalastat)
- A search of conference proceedings: American Society of Nephrology (ASN), American Society of Human Genetics (ASHG), Annual Clinical Genetics Meeting (ACGM), European Society of Human Genetics (ESHG), Fabry Nephropathy Update, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting, ISPOR Annual European Congress, Lysosomal Disease Network (LDN), Society for the Study of Inborn Errors of Metabolism (SSIEM).

Manual checking of the references lists of relevant systematic literature reviews was also carried out.

The grey literature searches were conducted using keywords similar to those used in the above database searches.

17.1.6 The inclusion and exclusion criteria.

	Population	**Interventions and Comparators**	**Outcomes**	**Study Design**
Inclusion criteria	• At least 10 adults with Fabry disease	• Any/all pharmacological therapies aimed at primary treatment of Fabry disease	**Clinical** • Efficacy, such as: ○ Renal function ○ Cardiac events ○ Cerebrovascular events ○ GL-3 levels • Safety and tolerability, such as: ○ Overall, severe, or serious AEs ○ Discontinuations (all cause, due to AEs, due to lack of efficacy) ○ Mortality	• Prospective interventional trials (including RCTs) • Observational studies (including patient registries) • Retrospective analyses • Modeling studies • Economic analyses

			Quality of life, such as: • SF-36 • EQ-5D • Pain **Economic,** such as: • Direct and indirect costs • Cost-effectiveness (QALYs, ICERs) • Productivity • Resource utilization	
Exclusion criteria	• Patients with conditions other than Fabry disease	• Non-pharmacological treatment • Treatment of sequelae of Fabry disease • Non-approved doses or schedules of treatment for Fabry disease • No treatment intervention (for studies reporting clinical outcomes)	• No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes • Outcomes not reported for Fabry patients only in studies with a mixed population	• Narrative literature reviews, expert opinions, letters to the editor, editorials, or consensus reports • Case reports or case series of fewer than 10 patients • *In vitro*, animal, genetic, or fetal studies • Studies reporting only pooled data for patients from multiple study designs (RCTs, registries, open-label extensions) • Studies reporting treatment switching between types of ERT

17.1.7 The data abstraction strategy.

Records identified from the searches (literature databases and grey literature searches) underwent two rounds of screening according to the inclusion/exclusion criteria. No study was excluded at abstract-level screening due to insufficient information.

In the first round, two investigators independently evaluated the titles/abstracts of all unique records based on the specified inclusion/exclusion criteria. Following the review of titles/abstracts, all publications meeting the study inclusion criteria were retrieved and independently reviewed in full text by two investigators. None of the exclusion criteria and all of the protocol-specified inclusion criteria had to be met for a study to pass this round. During both rounds of the screening process, discrepancies were resolved through consensus, and a third investigator resolved any disagreement between the two investigators.

Articles were excluded based on language. Non-English-language articles accepted at the abstract level were not further evaluated.

Data on the outcomes of interest were extracted from each included study by a single researcher and validated for accuracy by a second, senior researcher. To ensure quality and consistency of data, the full data extraction form was piloted, with multiple reviewers using it to extract data from several included studies. During this pilot phase, differences in the interpretation or potential ambiguities were identified and resolved through consensus within the team. All reviewers were provided with succinct written instructions, and a senior staff member addressed any questions that arose during the process.

Literature identified from all sources was cross-checked to identify related records. In the event that data discrepancies were noted between sources, priority was given in the following order:

1. Data used in submissions to regulatory agencies
2. Data from full-text, peer-reviewed publications
3. Data from unpublished internal sources (Amicus' clinical study reports or unpublished manuscripts)
4. Data reported in conference abstracts

Specific outcomes that were captured reflect the final NICE scope and include:

Clinical:

- Symptoms of Fabry disease (including pain)
- Gb3 levels in kidney and urine
- Renal function
- Cardiac function
- Progression-free survival (time to occurrence of renal, cardiac, neurological and cerebrovascular events)
- Mortality
- Adverse effects of treatment

Quality of life, such as:

- SF-36
- EQ-5D
- Pain

Economic, such as:

- Direct and indirect costs
- Cost-effectiveness (QALYs, ICERs)
- Productivity
- Resource utilization

17.2 Appendix 2: Search strategy for adverse events

The following information should be provided.

17.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

See Section 17.1.1

17.2.2 The date on which the search was conducted.

See Section 17.1.2

17.2.3 The date span of the search.

See Section 17.1.3

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See Section 17.1.4

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 17.1.5

17.2.6 *The inclusion and exclusion criteria*.

See Section 17.1.6

17.2.7 The data abstraction strategy.

See Section 17.1.7

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *EconLIT*
- *NHS EED.*

See Section 17.1.1

17.3.2 The date on which the search was conducted.

See Section 17.1.2

17.3.3 The date span of the search.

See Section 17.1.3

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See Section 17.1.4

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 17.1.5

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *NHS EED*
- *EconLIT.*

See Section 17.1.1

17.4.2 The date on which the search was conducted.

See Section 17.1.2

17.4.3 The date span of the search.

See Section 17.1.3

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See Section 17.1.4

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 17.1.5

17.4.6 The inclusion and exclusion criteria.

See Section 17.1.6

17.4.7 The data abstraction strategy.

See Section 17.1.7

18 Related procedures for evidence submission

18.1 Cost-consequence models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

Manufacturer response to ERG questions regarding migalastat for the treatment of Fabry disease in patients with amenable mutations [ID868]

Section A: Clarification on effectiveness data

A1. The results of the Fabry Infusion Survey (UK) which are reported in the submission (pages 46-50) and in the Fabry Infusion Survey document (provided by the company as a confidential PDF file) appear to be for selected questions only. Of 53 questions only 22 questions are mentioned, indirectly, in the Fabry Infusion Survey document. To help us interpret these results please would the company:

(i) provide a list of the 53 questions which were asked in the survey.

(ii) explain why the results from some questions have not been presented.

(i) The Fabry Infusion Survey questionnaire is included in Appendix 1.

(ii) Data from the report relevant to the quality of life of UK Fabry patients were presented in the submission. Some of the data collected were not of direct relevance to the submission or were not considered generalizable for patients in the UK. Where not presented in the submission, the majority of data are available in the Fabry Infusion Survey report that has been cited as a reference (Table 1).

Table 1. Reporting of data from Fabry Infusion Survey

Questions	Data collected	In submission	In Fabry Infusion Survey report	Not relevant to patients in the UK
1 - 13	Patient consent, patient information and demographics		Y	
14 - 17	Information on family members with Fabry disease and their requirements for ERT infusions		Y	
18 - 23	Treatment history		Y	
24 - 32	Treatment logistics	Y (infusion time)	Y (other aspects)	
33 - 35	Treatment experience	Y		
36 - 40	Impact on daily life (employment)	Y		
41 - 46	Impact on daily life (school)	Y (adult data)		Y (indication is age 16+)
47 - 49	Impact on daily life	Y		
50 - 53	Healthcare insurance and patient funding of ERT			Y

A2. Please explain what is meant by end-stage Fabry disease (company submission page 62). This is not explained in the cited reference by Biegstraaten 2015.

This is in relation to stopping criteria from European consensus group:
“End-stage Fabry disease or other comorbidities with life expectancy <1 year (class IIB)” where end-stage Fabry disease refers to patients who are unlikely not to survive more than a year so they would not derive benefit from treatment for their Fabry disease.

A3. The PRISMA flow chart in the company submission (Figure C9.1) states that 74 sources were included in the systematic review, some of which are described as publications and some of which are described as studies. These are further divided into 12 migalastat and 62 non-migalastat sources. No bibliography is provided for the latter.

(i) Please can the company supply a bibliography of the non-migalastat publications, preferably with publications linked according to their respective studies.

(ii) For what purpose was the inclusion of the non-migalastat studies?

(i) See Appendix 2 for a list of the 62 publications split by type and a table linking publications to their studies.

(ii) The systematic literature review was designed to have broad inclusion/ exclusion criteria in order to ensure the comprehensive identification and abstraction of all clinical evidence relating to treatment of Fabry disease, including the comparators specified in the NICE scope. Comparator studies were not described in detail in the submission since direct active comparative evidence is available from the migalastat ATTRACT study. After an initial feasibility assessment, it was considered not feasible to use the identified studies from the systematic literature review to enable the development of a network meta-analysis.

A4. Table C9.6 appears to identify only 11 of the 12 migalastat reference sources indicated in the PRISMA chart. We assume this is because Amicus Therapeutics 2015c is not included in the table.

(i) Please confirm if this is correct, or whether any other references are missing.

(ii) Please provide a copy of the reference for Hughes et al., 2015 cited in Table C9.6 (page 91), as we have not received any references which match this citation. Should Hughes et al., 2015 be academic in confidence?

(i) There are 12 reference sources in Table C9.6, although it may not be clear due to the way the table is formatted. A list of the 12 studies is provided below.

1. Amicus Therapeutics, 2015a. Data on File: Clinical Study Report. AT1001-011 (FACETS),
2. Amicus Therapeutics, 2015b. Data on File: Interim Clinical Study Report. AT1001-012 (ATTRACT),
3. ATTRACT Draft Manuscript, Oral Pharmacological Chaperone Migalastat compared to Enzyme Replacement Therapy for Fabry Disease: 18-Month Results from the Phase 3 ATTRACT Study. , pp.1–24.
4. Benjamin, E. et al., 2015. Migalastat Reduces Plasma Globotriaosylsphingosine (lyso- Gb3) in Fabry Patients : Results from Phase 3 Clinical Studies. Paper presented at: Annual Clinical Genetics Meeting, p.Abstract 741.
5. Bichet, D. et al., 2014. Subjects treated with Migalastat continue to demonstrate stable renal function in a Phase 3 extension study of Fabry Disease. presented at: American Society of Human Genetics 2014. Presented at: the American Society of Human Genetics (ASHG) Conference.
6. Germain, D. et al., 2015a. Phase 3 and long-term extension study with migalastat, a pharmacological chaperone, demonstrate stable renal function, reduced left ventricular mass and gastrointestinal symptom improvement in patients with Fabry disease. Presented at ASHG Annual Meeting. Presented at ASHG Annual Meeting, p.Abstract 474W.

7. Germain, D. et al., 2015b. Subjects treated with migalastat continue to demonstrate stable renal function and reduced left ventricular mass index over 3 years in a long-term extension study of Fabry. Presented at SSIEM Annual Meeting. J Inherit Metab Dis, p.Abstract O–050.
8. Germain, D. et al., 2015c. Subjects treated with migalastat demonstrate stable renal function, reduced left ventricular mass and gastrointestinal symptom improvement in Phase 3 and a long-term extension study of Fabry Disease. Paper presented at: ESHG 2015. ESHG, p.Abstract PM06.10.
9. Germain, D.P., Hughes, D. & Nicholls, K., (Submitted Manuscript) Efficacy and Safety of Migalastat, an oral Pharmacological Chaperone for Fabry Disease.
10. Hughes, D. et al., 2015. Long-term efficacy and safety of migalastat compared to enzyme replacement therapy in Fabry disease: Phase 3 study results. presented at: Lysosomal Disease Network 2015. Molecular Genetics and Metabolism, 114, p.Abstract 115.
11. Nicholls, K.M. et al., 2014. Migalastat and Enzyme Replacement Therapy Have Comparable Effects on Renal Function in Fabry Disease : Phase 3 Study Results. Presented at: American Society of Nephrology 2014. J Am Soc Nephrol, 25, p.Abstract SA–PO1098.
12. Schiffmann, R. et al., 2015. Improvement in gastrointestinal symptoms observed in the phase 3 FACETS (AT1001-011) study of migalastat in patients affected with Fabry disease. Paper presented at: Lysosomal Disease Network 2015. Molecular Genetics and Metabolism, 114, p.Abstract 230.

(ii) A copy of the Hughes et al., 2015 abstract has been provided with this response. It is not academic in confidence.

A5. It is stated that randomisation was conducted by interactive voice response system in the ATTRACT trial, and by use of a central randomisation system in the FACETS trial (Table C9.12). Please can the company provide further detail on the method used for the *sequence generation* in both trials. In particular, please could more information be provided about the interactive voice response system, and whether this is used to generate a random sequence generation (e.g. by computer random number generator).

For the FACETS trial, the interactive voice response system (IVRS) was provided by Cenduit who also generated randomisation blocks as defined in user requirement specifications, in the following manner:

- Two treatment groups: Placebo or migalastat
- Stratification groups: Male or female
- Specifications including selection method, block size, number of blocks to generate and maximum consecutive repetitions, to randomly assign treatment codes
- A test file with above was generated for Amicus to review and sign off on
- A final randomisation file was generated and but not provided to Amicus to ensure Sponsor remained blinded to treatment blocks
- These randomisation blocks were used at the backend of the IVRS system when the site accessed IVRS through telephone or internet, to randomise successfully screened patients
- At time of unblinding, the randomisation file was transmitted directly from Cenduit to the biostatistician at Quintiles, for statistical analysis purposes

For the ATTRACT trial, a similar process to above was used, but stratified by both sex and protein levels, and provided by a different vendor (Almac).

A6. Please could the company clarify its critical appraisal judgement for the adequacy of the concealment of treatment allocation in Table C9.12 for the ATTRACT trial. The current response appears to relate to blinding, which is distinct from the concealment of the random allocation process.

Although ATTRACT was an open-label study, the same process was used as in a blinded study, where the IVRS vendor created a randomisation file to create random treatment codes stratified by sex and protein levels, assigning subjects to either migalastat or enzyme replacement therapy via these randomly generated blocks.

Similar to a blinded study, at the end of the 18-month treatment period, the randomisation file was transmitted directly from Almac to the biostatistician at Quintiles, for statistical analysis purposes, without ever being sent to Amicus as the Sponsor.

A7. **High priority**: Was the quality assessment of the migalastat RCTs done by a single reviewer, or was it checked by a second reviewer, or independently performed by two reviewers (Table C9.12)?

The quality assessment was performed by a single reviewer and checked by a second reviewer, rather than being performed by two reviewers independently in parallel.

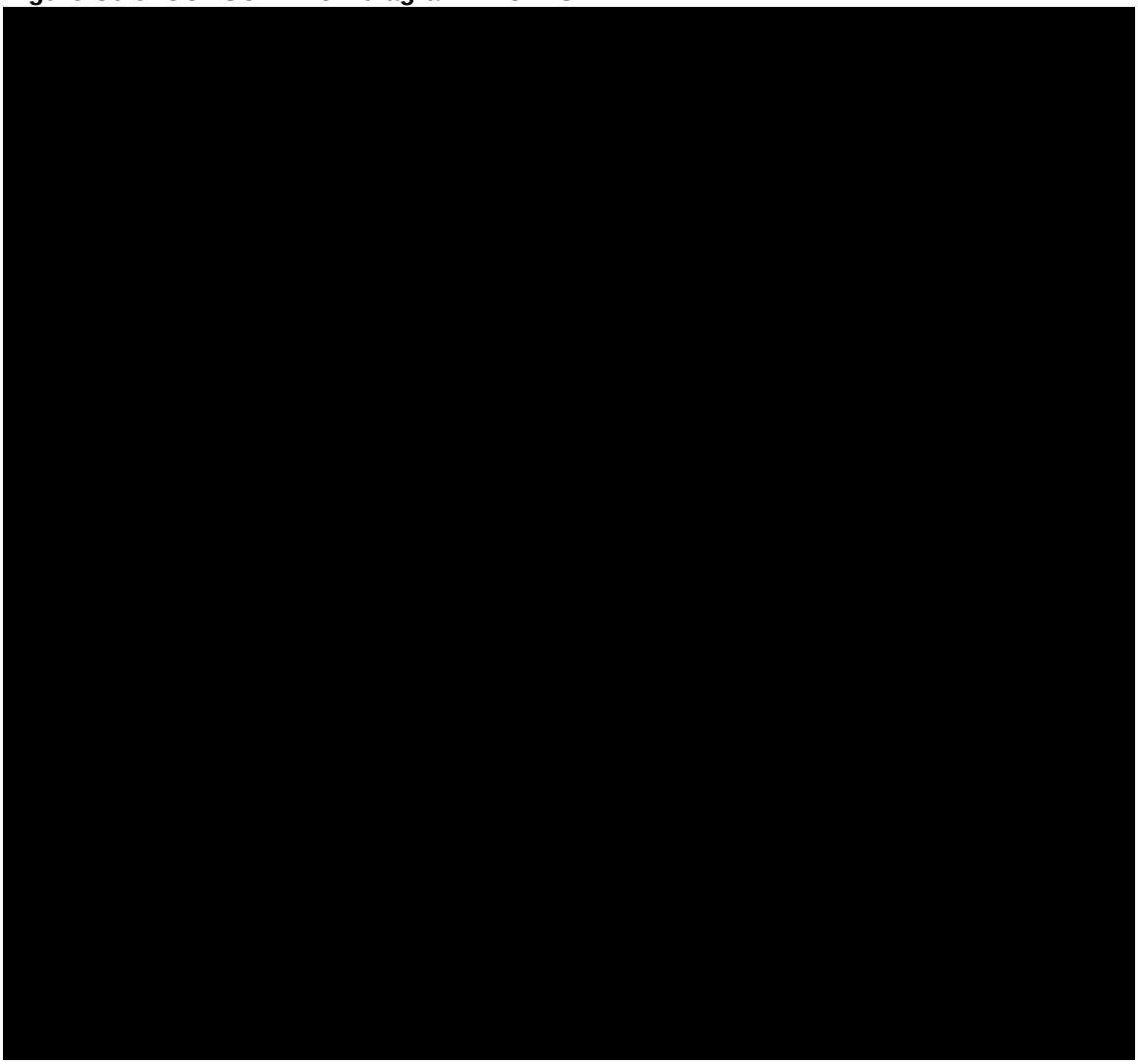
A8. The CONSORT flow chart for the ATTRACT study (Figure C9.5) shows that [redacted] We assume that this is an error since the numbers in the table do not sum to [redacted]. Please confirm which number is correct.

There is an error in Table C9.11. The number of patients randomised to migalastat and included in the ITT population was [redacted].

A9. The CONSORT flow chart for the FACETS study reported in Figure C9.6 shows that [redacted]. According to the FACETS unpublished manuscript (supplementary material) the number in this arm [redacted]. We assume [redacted] is an error [redacted]. Please confirm which number is correct.

The CONSORT diagram is incorrect. The number of patients in the migalastat arm completing stage 2 was [redacted]. An updated CONSORT flow chart is provided below.

Figure C9.6: CONSORT flow diagram FACETS



A10. In section 9.8 (p. 124) the company submission states that a systematic review and feasibility assessment was conducted for a potential network meta-analysis. A total of eight RCTs from the systematic review were initially deemed relevant for inclusion in the feasibility evaluation. Two of these were the ATTRACT and FACETS trials. However, it is unclear how the remaining six RCTs were identified based on the information in the PRISMA chart (Figure C9.1).

(i) Please clarify whether the six additional identified RCTs for network meta-analysis feasibility assessment were a subset of the 16 “non-migalastat” RCTs in the PRISMA chart or, if not, where they were identified from.
(ii) Please clarify the inclusion and exclusion criteria that were applied to identify these six RCTs.

(i) Non-migalastat studies included in the feasibility assessment

In order to ensure adequate time to complete a network meta-analysis (should it have been possible) the feasibility assessment was based on an SLR that was carried out well in advance of finalisation of the NICE decision problem and scope. This SLR was wider in specification than defined in the NICE scope since those studies that used unlicensed doses or schedules of ERT or did not report the relevant outcomes of interest [per the finalised NICE scope] were not excluded.

In total 32 publications relating to 8 trials (including the 16 non-migalastat RCT publications in the PRISMA diagram in Figure C9.1) were considered in the feasibility assessment (Table 2 and Appendix 3). Note that 4 of secondary references (marked in bold) relate to more than one primary study (Benichou et al, 2009; Schiffmann et al, 2013; West et al, 2009; Benjamin et al, 2015) and are therefore duplicated in Table 2.

The 16 'non-migalastat' publications included in the final SLR and described in the PRISMA chart represent four of the six 'non-migalastat' RCTs (4 primary references and 12 linked publications, shaded grey in Table 2). Note again that 3 of the secondary references relate to more than one primary study (Benichou et al, 2009; Schiffmann et al, 2013; West et al, 2009).

The two additional non-migalastat RCTs (Hughes et al, 2013; Vedder et al, 2007) and their related publications identified in the initial SLR are not included in the 16 'non-migalastat' RCT publications in Figure C9.1 since they met the further exclusion criterion ("No outcomes of interest [per the finalized NICE scope]" and "Studies reporting non-approved dose or schedule of ERT") added to the SLR following the finalisation of the NICE scope. It should also be noted that these 2 studies were excluded from the feasibility analysis at an early stage for similar reasons (one was a dose comparison study, the other did not include a licensed dose regimen).

Table 2. Studies Explored in the Feasibility Assessment

Trial Name	Primary Reference (author, year)	Secondary Reference (study ID–author, year)
AGAL-008-00	Banikazemi, (2007)[1]	Fellgiebel, 2014[2]; **Benichou, 2009**[3]
AGAL-1-002-98	Eng, 2001[4]	Wilcox, 2004[5]; **Benichou, 2009[3];** Germain, 2007[6]; Thurberg, 2002[7]; Eng, 2001[8]; Thurberg, 2009[9]; and Thurberg, 2004[10]
NR	Hughes, 2013[11]	None
TKT 007	Hughes, 2008[12]	**Schiffmann, 2013[13]; West, 2009[14]**; Hajiof, 2003[15]; and Hajioff, 2003[16]
NR	Schiffmann, 2001[17]	**Schiffmann, 2013[13]; West, 2009[14];** Schiffmann, 2003[18]; Schiffmann, 2006a[19]; Schiffmann, 2006b[20]; Moore, 2002[21]; Moore, 2001[22]; and Moore, 2002[23]
ISRCTN45178534	Vedder, 2007[24]	Vedder, 2008[25]
FACETS	Germain, Under Review[26]	**Benjamin, 2015[27]**; Barlow, 2014[28]; Bichet, 2014[29]; and CSR[30]
ATTRACT	ATTRACT Draft Manuscript[31]	**Benjamin, 2015[27];** and CSR[32]
Reference citations can be found in Appendix 3**Appendix 3.**		

(ii) Inclusion exclusion criteria

The inclusion/exclusion criteria for trials assessed in the feasibility assessment were the same as those applied to studies reporting clinical outcomes in the overall SLR (summarised in Section 9 of the submission), with the two exceptions that 1) only publications of RCTs were evaluated (rather than observational studies, single-arm trials, etc.) in the feasibility

assessment, and 2) at the time that the feasibility assessment was conducted, publications of RCTs reporting on non-approved doses or schedules of ERT were included in the SLR.

A11. Page 126, Table C9.29: Please supply a reference list of the six RCTs referred to in the table.

The six references are:

1) ATTRACT Draft Manuscript, Oral Pharmacological Chaperone Migalastat compared to Enzyme Replacement Therapy for Fabry Disease: 18-Month Results from the Phase 3 ATTRACT Study. , pp.1–24.
2) Banikazemi, M. et al., 2007. Agalsidase-Beta Therapy for Advanced Fabry Disease: A Randomized Trial. Ann Intern Med, 146, pp.77–86.
3) Eng, C.M. et al., 2001. Safety and efficacy of recombinant human alfa galactosidase A replacement therapy in Fabry's disease. N Eng J Med, 345(1), pp.9–16.
4) Germain, D.P., Hughes, D. & Nicholls, K., (Submitted Manuscript) Efficacy and Safety of Migalastat, an oral Pharmacological Chaperone for Fabry Disease.
5) Hughes, D. et al., 2008. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart (British Cardiac Society), 94(2), pp.153–8.
6) Schiffmann, R. et al., 2001. Enzyme Replacement Therapy in Fabry Disease. JAMA, 285, pp.2743–2749.

Section B: Clarification on cost model and value for money

B1. **High Priority:** Please explain why the disutilities for infusions are larger than those that would be seen for a serious medical condition (e.g. stroke) and how these large disutilities can be justified.

The disutility for infusions used in the base case analysis was 0.052, which is not considered to be disproportional to the other disutilities within the migalastat economic model or have a greater disutility impact relative to other serious medical conditions. In fact, the disutility for infusions is smaller than the disutility for five of the six adverse events included in the analysis:

- Headache (0.078)
- Influenza (0.162)
- Dyspnoea (0.090)
- *Upper respiratory tract infection (0.018)**
- Urinary tract infection (0.053)
- Gastritis (0.130)

If the health state utilities used in the model are considered, patients with Fabry disease with no symptoms (asymptomatic) have a utility of 0.874 whilst patients with Fabry disease that have a stroke have a utility of 0.744, equating to a utility decrement for stroke of 0.13, which is greater than the value of the ERT infusion disutility.

There is limited evidence of the quality of life or disutility impact surrounding different modes of administration of treatments. Boye et al (2011) examined the utilities and disutilities for attributes of injectable treatments for type 2 diabetes. They found that, compared to oral treatments, the utility difference for injectable treatments was between 0.07 and 0.17 in favour of oral treatments, depending on the frequency and whether there were injection site

reactions. In the NICE appraisal of fingolimod (TA 254) for the treatment of relapsing-remitting MS, the disutility associated with injectable disease modifying treatments was modelled as 0.035 so the estimate of 0.052 for ERT infusion is of a similar magnitude and has face validity and logical consistency.

B2. **High Priority:** The disutility for infusions appears to continue indefinitely whilst patients are on treatment, please provide justification for this assumed duration.

The discrete choice experiment for Fabry disease did not apply any time limit to the attributes. The descriptions included:

- Treatment is through an infusion which is taken once every two weeks. The infusion must be made up fresh and can be done by the patient themselves at home. It requires clean (antiseptic) preparation. The treatment would be delivered to your home and stored in your fridge. Each infusion would take on average 90-240 minutes.
- Treatment is through an infusion which is taken once every two weeks. The infusion must be made up fresh and is undertaken by a nurse who comes to your home. It requires clean (antiseptic) preparation. The treatment would be delivered to your home and stored in your fridge. Each infusion would take on average 90-240 minutes.

In some other diseases, patients may accommodate to their deteriorated health status over time e.g. blindness. However, it is logical that patients with Fabry disease will always experience a level of inconvenience over the duration of ERT treatment.

The disutility specifically relates to the preparation, administration, storage and duration of infusions. These factors will not change regardless of the length of time a patient has been on treatment, and therefore the burden placed on patients by these factors will not reduce over time.

In the NICE appraisal of fingolimod (TA 254) for the treatment of relapsing-remitting MS, the disutility for injectable disease modifying treatments was modelled over the duration of the treatment.

B3. After patients reach any two-complication health state, treatment appears to have no further effect on disease progression. Please provide the rationale for this assumption. Given that treatment appears to have no further effect, please justify the need for treatment in this patient group.

The transition probabilities with ERT obtained from Rombach et al (2013) were based on the corresponding publication from the same authors on the long-term effectiveness of ERT (Rombach, Smid, et al. 2013). This publication only found a treatment effect (presented as odds ratios in Table 4 of the publication) on the time to developing first and second complications. In their study population, only nine patients were still alive after the second complication, four developed a third complication or died, all within 6 years; two with and two without treatment. Therefore, they would not have been able to detect a treatment effect of ERT on the progression to third complication or death because of small patient numbers. In light of the lack of data, Rombach and colleagues have therefore assumed in their modelling framework that there is no treatment effect once patients have a second complication. This is a conservative approach and underestimates the benefit of treatments in Fabry disease due to the multi-systemic nature of the disease that would apply to both ERT and migalastat equally.

Therefore Amicus Therapeutics Ltd suggest that the decision to continue treatment should be based on clinical expert evaluation, since the benefit of remaining on treatment is specific to each individual patient. The existing ERT guidelines provide some recommendations for stopping rules i.e. when to consider taking patients off treatment (Table B8.2 of the submission).

Although Amicus Therapeutics Ltd has attempted to accurately model the health costs and outcomes for different treatment interventions for Fabry disease, it is not possible to reflect all the permutations of individual complications which determine if a patient should be continued to be treated with ERT or not (because of data availability and/or the modelling framework).

Importantly, there is no reason why a patient treated with migalastat would be assessed differently to a patient with ERT and therefore in instances when patients are currently benefiting from ERT when they have multiple complications, it is likely these patients would equally benefit from migalastat. Amicus Therapeutics Ltd has verified this with a clinical expect who has stated that:

"I completely agree that all patients should be assessed individually at each stage of the disease as there is insufficient data to support generalised management."

B4. In Table D12.16, the value reported for chronic kidney disease (stage 5) does not appear to match the Reference costs with the codes and description given. Please check and confirm that the description and codes are correct.

The codes are correct but there was a typographical error in the calculation of the weighted average. The cost should be £2,471.87 rather than £3,062.87. Adjusting for this error in the base case analysis results in total incremental costs of migalastat compared to ERT of £1,268,673.79 rather than £1,268,673.71, thus a negligible impact on the incremental results.

B5. In Table D12.16, the Reference costs codes for atrial fibrillation have been counted twice in the calculation of cardiac complications. Please explain why this is.

Unit costs of a rhythm disturbance requiring hospitalisation (as defined by Rombach et al (2013) could not be obtained from NHS reference costs. Therefore, the cost of atrial fibrillation was used as a proxy for the cost of a rhythm disturbance requiring hospitalisation. Consequently, the reference costs codes for atrial fibrillation have been counted twice in the calculation of cardiac complications – once to represent atrial fibrillation and secondly to represent a rhythm disturbance requiring hospitalisation.

Counting the cost only once would have a very negligible impact on the incremental cost results.

B6. In Table D12.16, please explain how the 'weights applied' in the last column of the table have been derived.

The weights applied are based on the number of Finished Consultant Episodes (FCEs) from the NHS reference costs. Thus the distribution of events within each health state in Fabry patients is assumed to be the same as the distribution of events within the general population.

B7. In table D.12.10, the values for TEAEs are reported in the submission to be based on the ERT and migalastat arms of the ATTRACT trial and cross refer to Table C9.28. However, the values in these tables do not appear to match; please clarify how the values in Table D12.10 have been derived.

The cross-reference should have been to the ATTRACT safety population adverse events in Table C9.27 of the submission. The number of patients experiencing events in the ATTRACT safety population (n=21 in the ERT arm and n=36 in the migalastat arm) was adjusted for exposure (476.67 days in the ERT arm and 522.19 days in the migalastat arm). There was a typographical error in the calculation of the annualised probabilities of dyspnoea and urinary tract infection. The corrected probabilities are included in Table 3.

Adjusting for this error in the base case analysis results in total incremental costs of migalastat compared to ERT of £1,268,675.35 rather than £1,268,673.71, thus a negligible impact on the incremental results.

Table 3. Calculation of annualized adverse event probabilities

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

Section C: Textual clarifications and additional points

C1. The manuscript for the ATTRACT study and two documents on the FACETS study (the Germain et al. manuscript and supplementary material) are not marked as academic in confidence. Please clarify whether they should be.

Yes, the draft manuscripts are academic in confidence.

The following references are commercial in confidence:

- Amicus Therapeutics (2015a) Data on File: Clinical Study Report. AT1001-011 (FACETS)
- Amicus Therapeutics (2015b) Data on File: EMA Submission - 2.5 Clinical Overview
- Amicus Therapeutics (2015c) Data on File: EMA Submission - Summary of Clinical Efficacy (2.7.3)
- Amicus Therapeutics (2015d) Data on FIle: Interim Clinical Study Report. AT1001-012 (ATTRACT)
- Amicus Therapeutics (2016c) Draft Galafold Summary of Product Characteristics
- Amicus Therapeutics (2016b) Data on File: Why Not Do a Network Meta-Analysis of Treatments for Fabry Disease?

The following references are academic in confidence:

- Amicus Therapeutics (2015e) Data on File. Fabry Infusion Survey: Results Report Based on Separate Analyses of US , UK and Canada Cohort Data
- Amicus Therapeutics (2016a) Data on File: Fabry UK Interview Report
- ATTRACT Draft Manuscript. Oral Pharmacological Chaperone Migalastat compared to Enzyme Replacement Therapy for Fabry Disease: 18-Month Results from the Phase 3 ATTRACT Study. pp. 1–24
- Germain, D.P., Hughes, D. and Nicholls, K. (Submitted Manuscript) Efficacy and Safety of Migalastat, an oral Pharmacological Chaperone for Fabry Disease.
- Germain, D.P., Hughes, D. and Nicholls, K. (Supplementary Appendix) Efficacy and Safety of Migalastat, an Oral Pharmacological Chaperone for Fabry disease.
- Lloyd, A., Gallop, K. and Ali, S. (2016) Estimating the value of treatment for Fabry disease: A discrete choice experiment

C2. Information from the Fabry Infusion Survey is highlighted as academic-in-confidence on pages 50 and 66 of the submission but has not been included in the checklist of confidential information. Please make sure all confidential information is correctly recorded in the checklist document.

The checklist has been checked and amended and provided with this response.

C3. We would like you to reconsider the information labelled as confidential in your submission. NICE considers it essential that evidence on which the Evaluation Committee's decisions are based is publically available so that the process is as transparent as possible. As noted in section 3.1.24 of the Guide to the process of technology appraisal, information marked as confidential should be kept to an absolute minimum. At present, we consider that your submission does not meet this criterion and therefore the marking is not acceptable. Particular areas of concern include:

- Information labelled as academic-in-confidence relating to quality of life outcomes for people with Fabry disease (Fabry infusion survey and UK Fabry patient survey)
- Infusion disutilities (Amicus Therapeutics Ltd' discrete choice experiment)
- Data from migalastat clinical studies (open-label extensions of ATTRACT and FACETS).

Amicus Therapeutics Ltd is committed to the transparency of the NICE appraisal process in order to enable evidence-based decision-making. Therefore Amicus has kept confidential marking to a minimum and there is very little data designated as commercial in confidence. The majority of the marking is data that is academic in confidence as Amicus Therapeutics Ltd believes the intellectual property of other stakeholders in the Fabry community should be respected. The committee can have an open discussion regarding AIC data and therefore we feel that this will not limit the rigour of decision-making process. Amicus Therapeutics Ltd does understand that NICE may want to make all published documentation (including the manufacturer submission) as transparent as possible but, as detailed in the checklist of confidential data, it is expected that the Fabry infusion survey, UK Fabry patient survey, discrete choice experiment and open-label extensions of ATTRACT and FACETS will soon be published and cannot be unmarked at this present time. During the course of the appraisal process, Amicus Therapeutics Ltd will endeavour to work with NICE to release some of the AIC restrictions as the publications enter the public domain.

C4. The two unpublished patient surveys and the discrete choice experiment underpin some of the crucial assumptions made about patient preferences and health-related quality of life. At present, the academic-in-confidence marking is so extensive that we will not be able to transparently communicate the committee's decision-making to our stakeholders. The release of the bulk of the highlighted information would be unlikely to jeopardise future publication and, therefore, its academic-in-confidence status is not justified. Please reduce the confidential data from the patient surveys and the discrete choice experiment accordingly.

Please see response to question C3. We have kept the confidential marking to a minimum as far as possible; we will endeavour to revise the marking as soon as publications are approved and/or enter the public domain.

C5. In the checklist of confidential information you have stated that the results of the migalastat clinical studies are due to be published in 2016/17. Please confirm the anticipated publication dates; it is important that we know if publication will take place before the completion of the evaluation.

These publications are submitted and are 'in-press'. Publication of the FACETS study is anticipated in [redacted]. Publication of ATTRACT is not expected [redacted]. We cannot provide a more accurate estimation of the timelines for publication of the ATTRACT study results at this point in time, as it will depend on feedback from the peer review.

C6. Some information on the market uptake of migalastat and the size of the patient population has been marked as commercial in confidence. Please explain how these numbers were sourced and the rationale for marking them as commercial in confidence.

The future market shares and patient population are estimated based on previous market research studies and anticipated uptake of migalastat in the market. As a publicly traded company with competitors in the market it is therefore essential that these numbers remain commercial in confidential.

C7. Further to the recent CHMP positive opinion, please supply a copy of the draft European public assessment report.

A copy of the report has been supplied with this response.

References

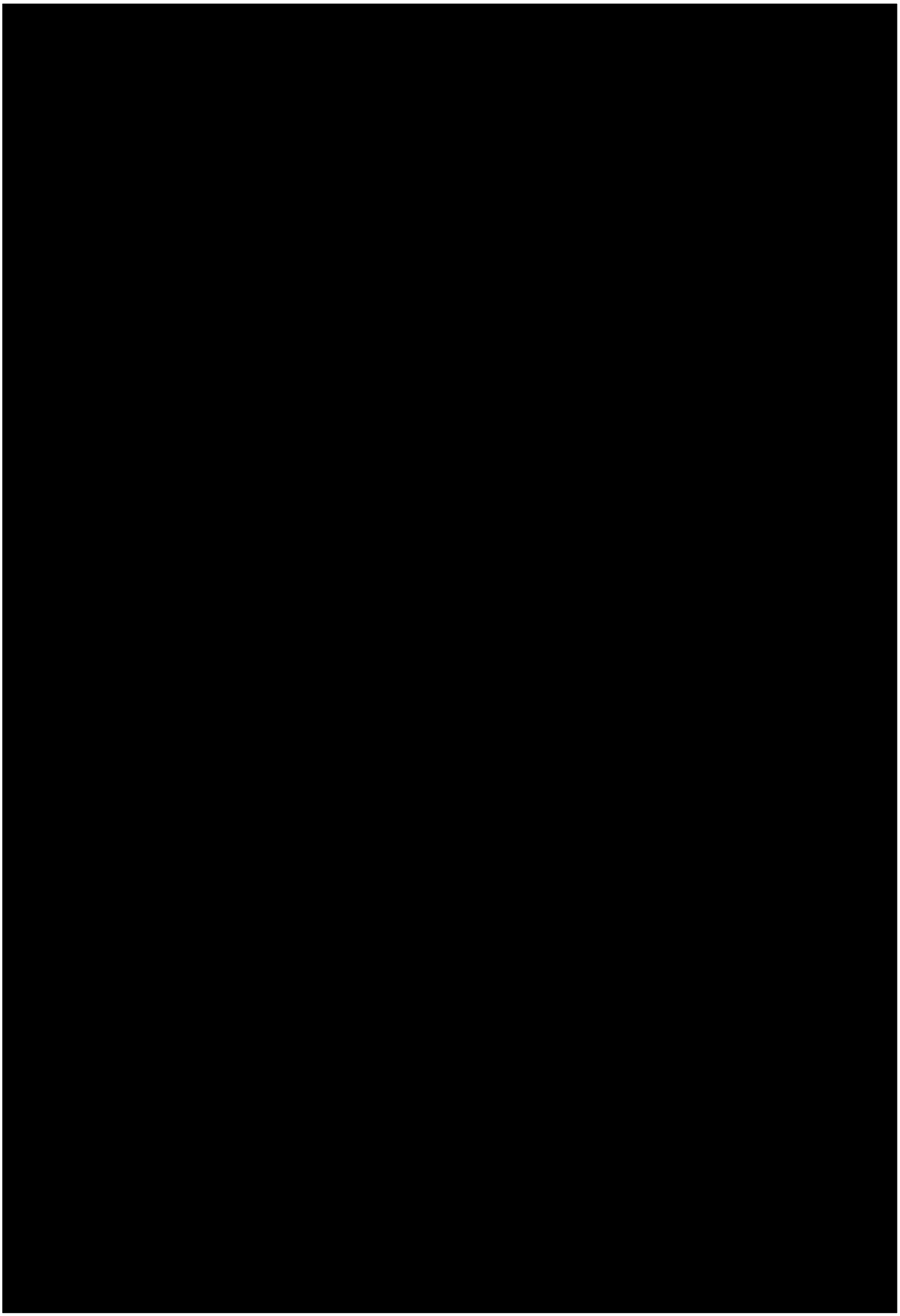
Banikazemi, M et al. 2007. “Agalsidase-Beta Therapy for Advanced Fabry Disease: A Randomized Trial.” *Ann Intern Med* 146: 77–86.

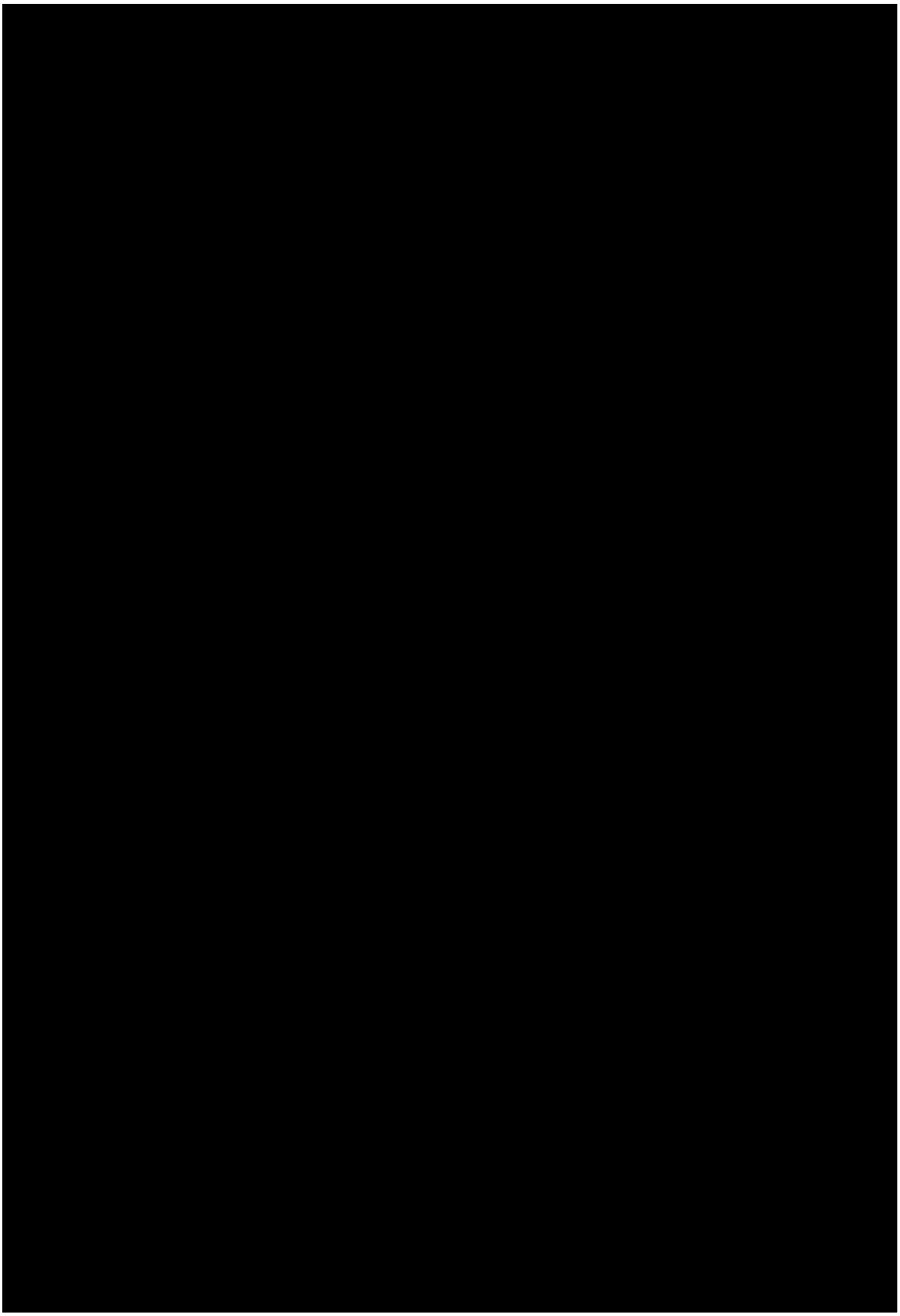
Boye, Kristina S. et al. 2011. “Utilities and Disutilities for Attributes of Injectable Treatments for Type 2 Diabetes.” *European Journal of Health Economics* 12(3): 219–30.

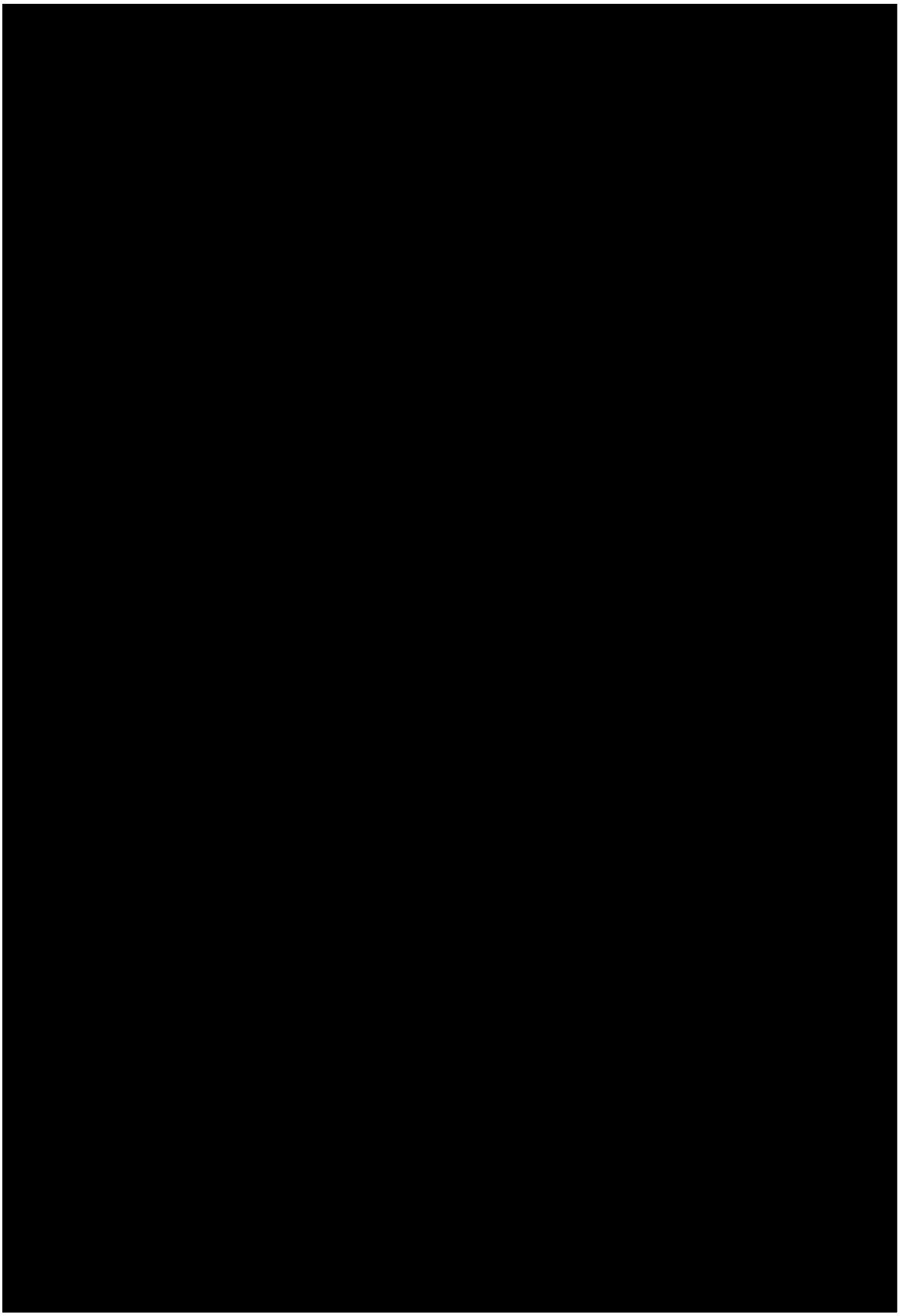
Rombach, Saskia M, Bouwien E Smid, et al. 2013. “Long Term Enzyme Replacement Therapy for Fabry Disease: Effectiveness on Kidney, Heart and Brain.” *Orphanet journal of rare diseases* 8(1): 47.

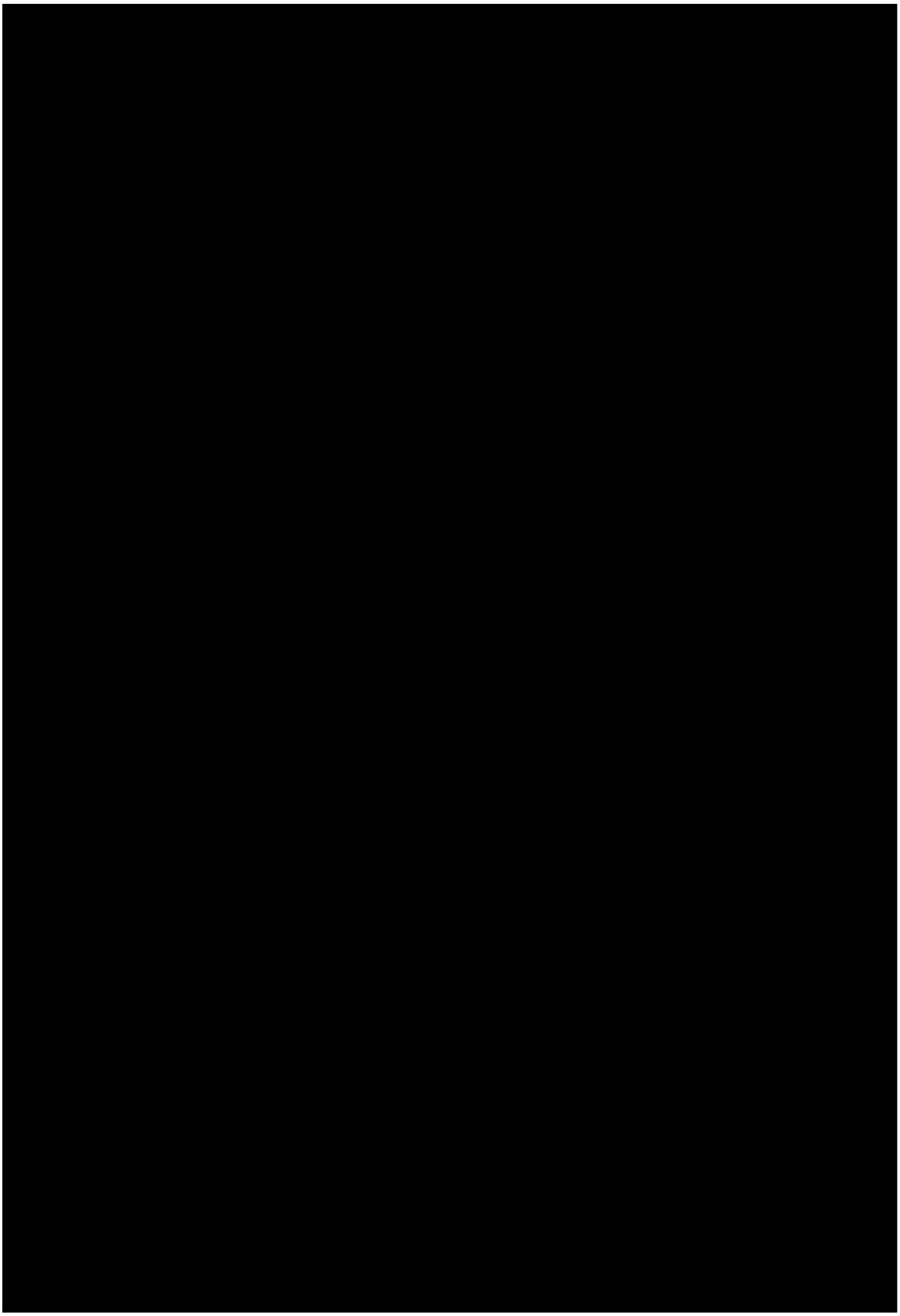
Rombach, Saskia M, Carla E M Hollak, Gabor E Linthorst, and Marcel G W Dijkgraaf. 2013. “Cost-Effectiveness of Enzyme Replacement Therapy for Fabry Disease.” *Orphanet journal of rare diseases* 8: 29.

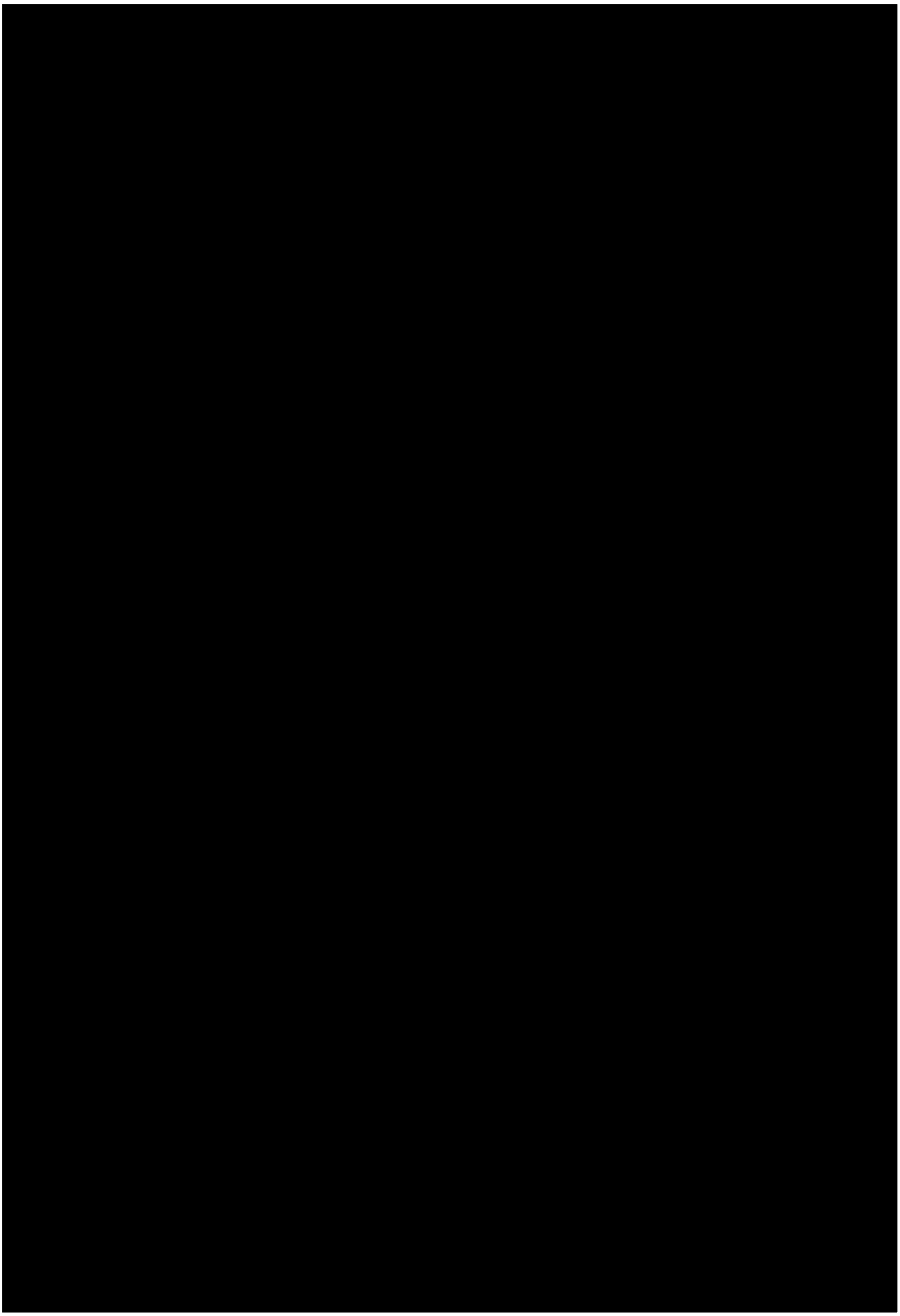
Appendix 1: Fabry Patient Experience Survey

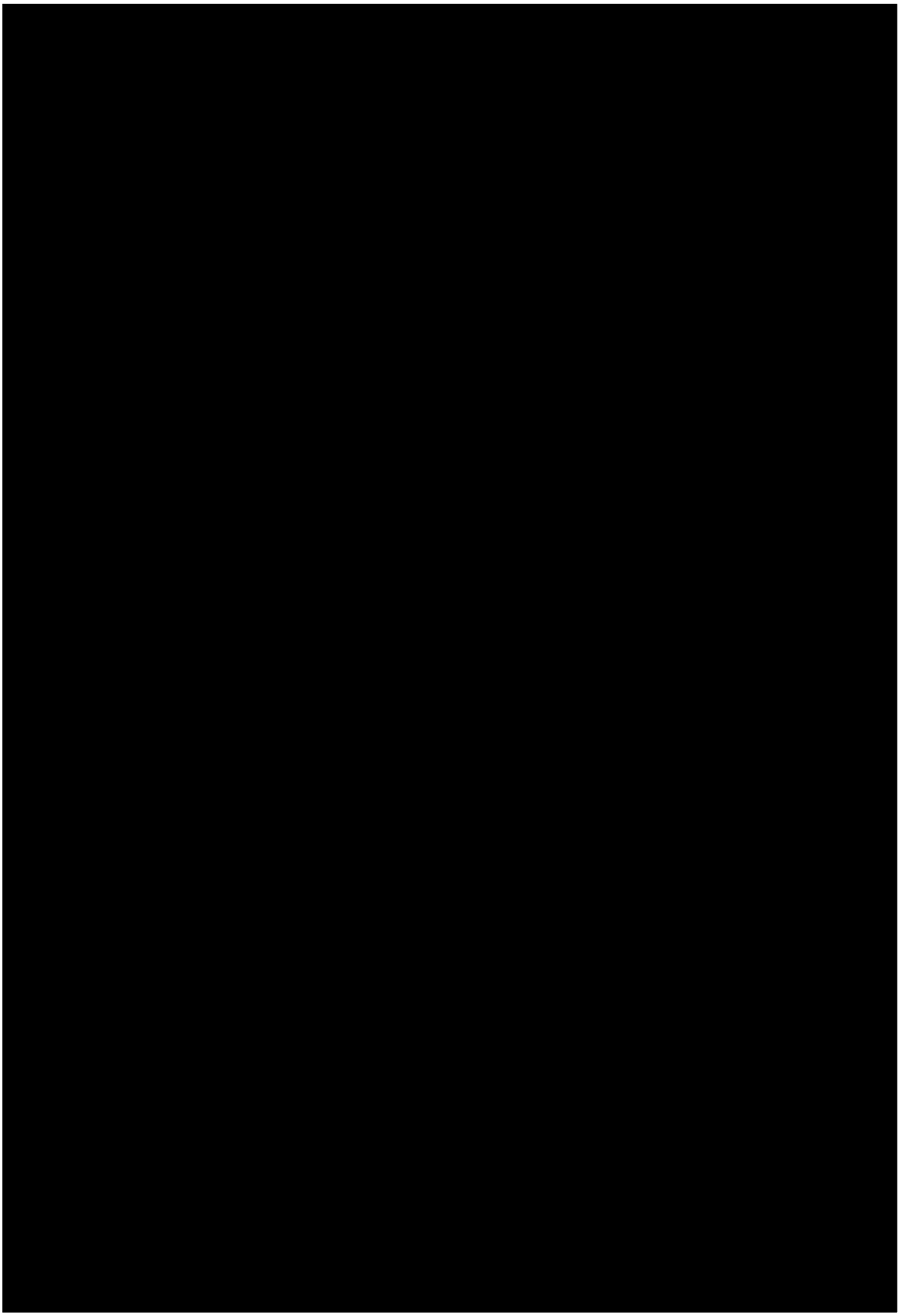


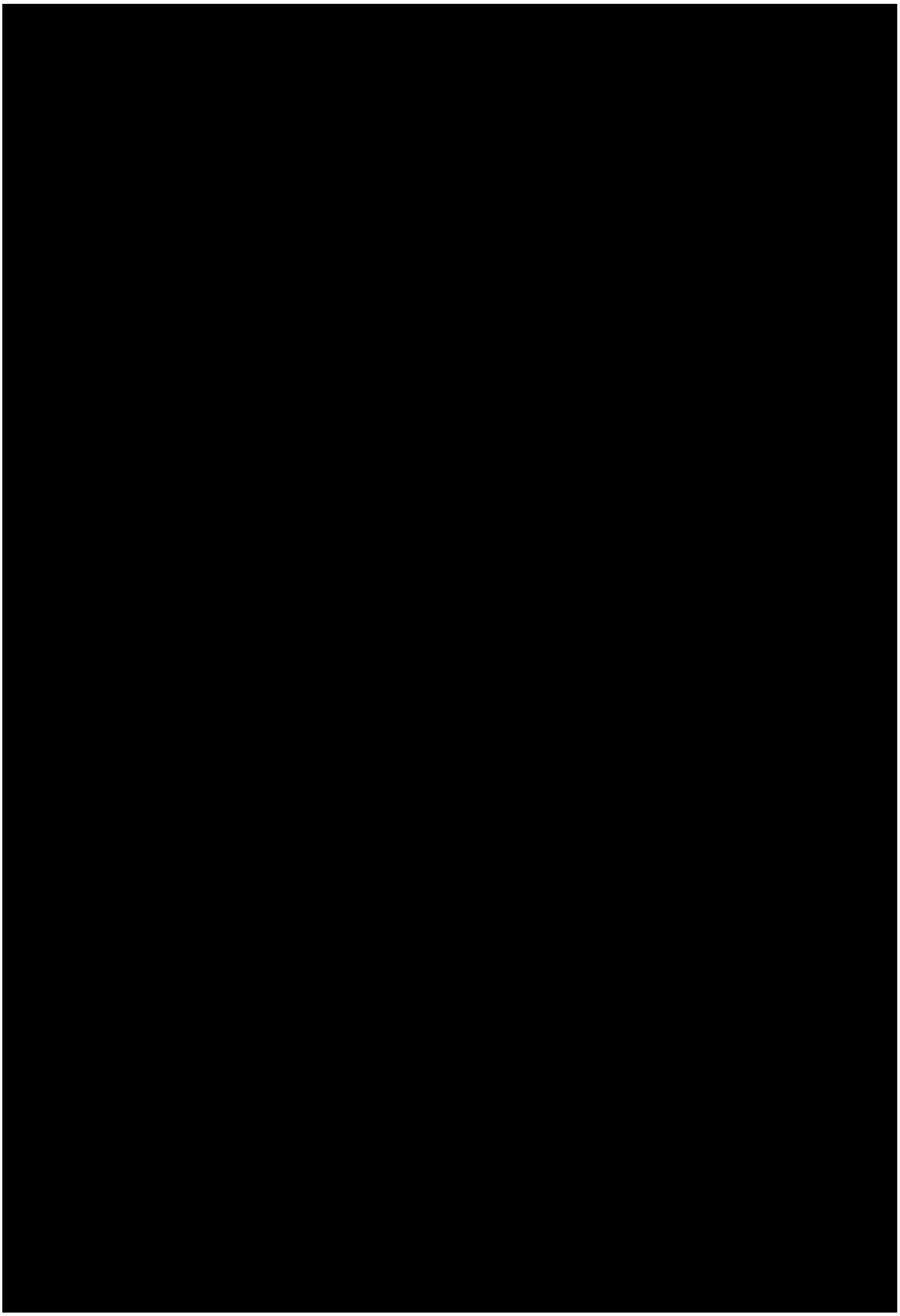


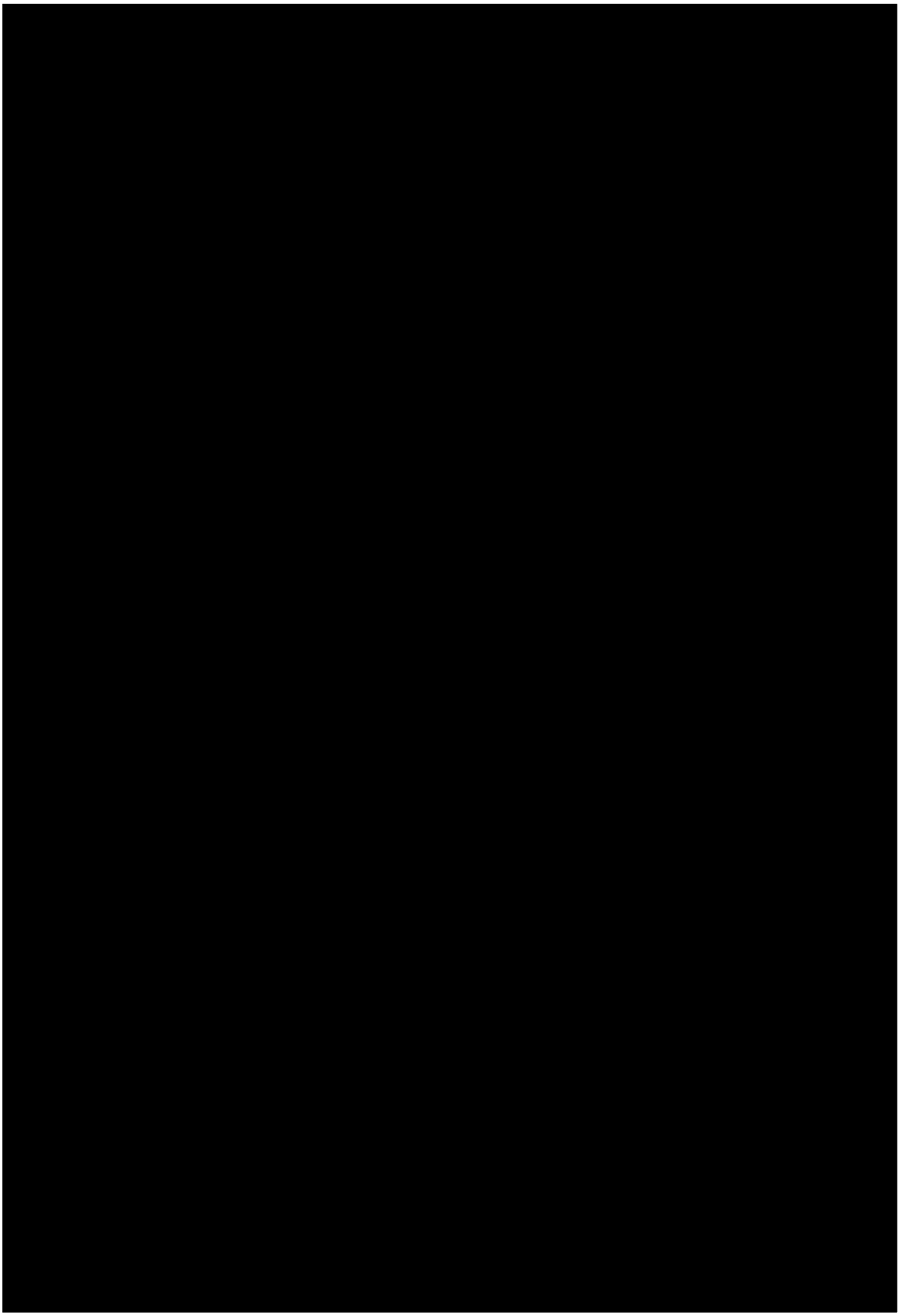












Appendix 2: List of Non-Migalastat publications identified in the Systematic Literature Review

INCLUDED OBSERVATIONAL CLINICAL STUDIES

1. Beck M, H, D., Kampmann, C., et al. Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: A Fabry Outcome Survey analysis. Paper presented at: Lysosomal Disease Network 2015.
2. Beck, M, Ricci R, Widmer U, et al. Fabry disease: overall effects of agalsidase alfa treatment. European journal of clinical investigation. Dec 2004;34(12):838-844.
3. Beer M, Weidemann F, Breunig F, Knoll A, Koeppe S, Machann W, et al. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. American Journal of Cardiology 2006;97(10):1515–8.
4. Breunig, F, Weidemann F, Strotmann J, Knoll A, Wanner C. Clinical benefit of enzyme replacement therapy in Fabry disease. Kidney international. Apr 2006;69(7):1216-1221.
5. Choi, JH, Cho YM, Suh KS, et al. Short-term efficacy of enzyme replacement therapy in Korean patients with Fabry disease. Journal of Korean medical science. Apr 2008;23(2):243-250.
6. Eto, Y, Ohashi T, Utsunomiya Y, et al. Enzyme replacement therapy in Japanese Fabry disease patients: the results of a phase 2 bridging study. Journal of inherited metabolic disease. 2005;28(4):575-583.
7. Feriozzi, S, Germain DP, Di Vito R, Legrand A, Ricci R, Barbey F. Cystatin C as a marker of early changes of renal function in Fabry nephropathy. Journal of nephrology. Jul-Aug 2007;20(4):437-443.
8. Hughes D, R, U., Mckie, M., et al. Fabry disease: Impact of ERT on renal function. Single-center 5-year results. Paper presented at: Lysosomal Disease Network 2015.
9. Kalliokoski, RJ, Kantola I, Kalliokoski KK, et al. The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease. Journal of inherited metabolic disease. Feb 2006;29(1):112-118.
10. Kampmann C, BS, Beck M,. Outcomes in Fabry disease patients after long-term agalsidase alfa enzyme replacement therapy (Abstract No. O-050). Paper presented at: SSIEM Annual Meeting 2015.
11. Kim JH, Cho JH, Lee BH, et al. Long-term efficacy of enzyme replacement therapy (ERT) for Fabry disease: experience of single institution. Presented at SSIEM Annual Meeting 2015.
12. Kisinovsky, I, Caceres G, Coronel C, Reisin R. Home infusion program for Fabry disease: experience with agalsidase alfa in Argentina. Medicina. 2013;73(1):31-34.
13. Lenders, M, Karabul N, Duning T, et al. Thromboembolic events in Fabry disease and the impact of factor V Leiden. Neurology. Mar 10 2015;84(10):1009-1016.
14. McKechnie D, Mac Lochlainn, DJ., Mehta, AB., Hughes, DA. Long term clinical outcomes in patients with Fabry disease receiving enzyme replacement therapy. Paper presented at: Lysosomal Disease Network 2015.
15. Parini, R, Rigoldi M, Santus F, et al. Enzyme replacement therapy with agalsidase alfa in a cohort of Italian patients with Anderson-Fabry disease: testing the effects with the Mainz Severity Score Index. Clinical genetics. Sep 2008;74(3):260-266.
16. Pastores, GM, Boyd E, Crandall K, Whelan A, Piersall L, Barnett N. Safety and pharmacokinetics of agalsidase alfa in patients with Fabry disease and end-stage renal disease. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. Jul 2007;22(7):1920-1925.
17. Prabakaran T, Birn, H., Nielsen, R., Christensen, EI.,. Long-term Enzyme Replacement Therapy is Associated with Reduced Poteinuria and Preserved Proximal Tubular Function in Women with Fabry Disease. Paper presented at: American Society of Nephrology 2013.
18. Shah, JS, Hughes DA, Sachdev B, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Dabry disease. American Journal of Cardiology. 2005;96(6):842-846.
19. Skrunes R, Tondel, C., Larsen, KK., Leh, S., Svarstad, E. Long-Term Enzyme Replacement Therapy (ERT) Benefits The Glomeruli More than the Vasculature in Younger Fabry Nephropathy. Paper presented at: 4th Update on Fabry Nephropathy 2015.
20. Taber T, Auray-Blais, C., Boutin, M., et al. Investigation of Biomarkers in Immune Response Against Human Recombinant Alpha-Gal A. Paper presented at: 4th Update on Fabry Nephropathy 2015.

21. Weidemann, F, Breunig F, Beer M, et al. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. Circulation. Sep 16 2003;108(11):1299-1301.
22. West M, Bichet, D., Casey, R., et al. Benefit of Enzyme Replacement Therapy in Fabry Disease: Comparison of Outcomes in the Canadian Fabry Disease Initiative Study. Paper presented at: 3rd Update on Fabry Nephropathy 2013.
23. West M, Bichet, D., Casey, R., et al. Clinical Effects of Neutralizing Anti-agalsidase Antibodies in Patients Receiving Enzyme Replacement Therapy in the Canadian Fabry Disease Initiative Study. Paper presented at: 3rd Update on Fabry Nephropathy 2013.
24. West ML, Bichet DG, Khan A, et al. Outcomes of patients over 65 in the Canadian Fabry Disease Initiative Study. Presented at ASN Kidney Week 2015.
25. Whybra, C, Miebach E, Mengel E, et al. A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. Genetics in medicine: official journal of the American College of Medical Genetics. Jun 2009;11(6):441-449.
26. Wyatt, K, Henley W, Anderson L, et al. The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: A longitudinal cohort study of people with lysosomal storage disorders. Health Technology Assessment. 2012;16(39):1-566.
27. Yoo H, Kim, WS., Lee, CH., et al. A Phase II Multicenter, Open-label Trial to Evaluate the Safety and Efficacy of Fabagal® (Agalsidase beta) in Patients with Fabry Disease. Paper presented at: American Society of Human Genetics 2014.

INCLUDED OBSERVATIONAL CLINICAL STUDIES WITH NO NEW RESULTS

1. Deegan, PB, Baehner AF, Barba Romero MA, Hughes DA, Kampmann C, Beck M. Natural history of Fabry disease in females in the Fabry Outcome Survey. Journal of medical genetics. Apr 2006;43(4):347-352.
2. Engelen, MA, Brand E, Baumeister TB, et al. Effects of enzyme replacement therapy in adult patients with Fabry disease on cardiac structure and function: A retrospective cohort study of the Fabry Munster Study (FaMuS) data. BMJ Open. 2012;2(6).
3. Hajioff, D, Hegemann S, Conti G, et al. Agalsidase alpha and hearing in Fabry disease: data from the Fabry Outcome Survey. European journal of clinical investigation. Sep 2006;36(9):663-667.
4. Hoffmann, B, Garcia de Lorenzo A, Mehta A, Beck M, Widmer U, Ricci R. Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). Journal of medical genetics. Mar 2005;42(3):247-252.
5. Hoffmann, B, Schwarz M, Mehta A, Keshav S. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. Dec 2007;5(12):1447-1453.
6. Hopkin R, Cabrera, G., Charrow, J., et al. Risk factors for severe clinical events and the incidence of these events in male and female patients with Fabry disease treated with agalsidase beta. Paper presented at: Lysosomal Disease Network 2015.
7. Hughes, DA, Barba Romero MA, Hollak CE, Giugliani R, Deegan PB. Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS--the Fabry Outcome Survey. Molecular genetics and metabolism. Jul 2011;103(3):207-214.
8. Mehta, A, Beck M, Elliott P, et al. Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet (London, England). Dec 12 2009;374(9706):1986-1996.
9. Mehta, A, Clarke JTR, Giugliani R, et al. Natural course of Fabry disease: Changing pattern of causes of death in FOS - Fabry Outcome Survey. Journal of medical genetics. 2009;46(8):548-552.
10. O'Mahony, C, Coats C, Cardona M, et al. Incidence and predictors of antibradycardia pacing in patients with Anderson-Fabry disease. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2011;13.
11. Ortiz A, Cabrera, GH., Charrow, J., et al. Occurrence of severe clinical events by time on agalsidase beta among patients with Fabry disease. Paper presented at: Lysosomal Disease Network 2015.

12. Talbot A, Nicholls, KM. Severity of Fabry Nephropathy as a Marker of Cardiovascular Outcome: 10-Year Data from an Australian Cohort on Enzyme Replacement Therapy. Paper presented at: American Society of Nephrology 2014.
13. Warnock D, Maruti, SS., Cabrera, GH., et al. Occurrence of Severe Clinical Events by Time on Enzyme Replacement Therapy with Agalsidase Beta among Patients with Fabry Disease. Paper presented at: American Society of Nephrology 2014.
14. Whybra, C, Kampmann C, Krummenauer F, et al. The Mainz Severity Score Index: A new instrument for quantifying the Anderson - Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clinical genetics. 2004;65(4):299-307.
15. Wilcox, WR, Linthorst, GE, Germain DP, et al. Anti-alpha-galactosidase A antibody response to agalsidase beta treatment: data from the Fabry Registry. Mol Genet Metab. 2012; 105:443-9
16. Wilcox, WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Molecular genetics and metabolism. Feb 2008;93(2):112-128.

INCLUDED NON-MIGALASTAT (ERT) RANDOMIZED CONTROLLED TRIALS

1. Banikazemi, M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Annals of internal medicine. Jan 16 2007;146(2):77-86.
2. Benichou, B, Goyal S, Sung C, Norfleet AM, O'Brien F. A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease. Molecular genetics and metabolism. Jan 2009;96(1):4-12.
3. Eng, CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human (alpha)-galactosidase a replacement therapy in Fabry's disease. New England Journal of Medicine. 2001;345(1):9-16.
4. Fellgiebel, A, Gartenschlager M, Wildberger K, Scheurich A, Desnick RJ, Sims K. Enzyme replacement therapy stabilized white matter lesion progression in fabry disease. Cerebrovascular Diseases. 2014;38(6):448-456.
5. Genzyme. A Study of the Safety and Efficacy of Fabrazyme in Patients With Fabry Disease (NCT00081497). 2015. Available at: https://clinicaltrials.gov/ct2/show/record/NCT00081497?term=fabry&rank=33&sect=X01256. Accessed August 2015.
6. Hajioff, D, Enever Y, Quiney R, Zuckerman J, Mackermot K, Mehta A. Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. Journal of inherited metabolic disease. 2003;26(8):787-794.
7. Hajioff, D, Goodwin S, Quiney R, Zuckerman J, MacDermot KD, Mehta A. Hearing improvement in patients with Fabry disease treated with agalsidase alfa. Acta paediatrica (Oslo, Norway : 1992). Supplement. Dec 2003;92(443):28-30; discussion 27.
8. Hughes, DA, Elliott PM, Shah J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart (British Cardiac Society). Feb 2008;94(2):153-158.
9. Schiffmann, R, Floeter MK, Dambrosia JM, et al. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. Muscle & nerve. Dec 2003;28(6):703-710.
10. Schiffmann, R, Hauer P, Freeman B, et al. Enzyme replacement therapy and intraepidermal innervation density in Fabry disease. Muscle & nerve. Jul 2006;34(1):53-56.
11. Schiffmann, R, Kopp JB, Austin HA, 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. Jama. Jun 6 2001;285(21):2743-2749.
12. Schiffmann, R, Ries M, Blankenship D, et al. Changes in plasma and urine globotriaosylceramide levels do not predict Fabry disease progression over 1 year of agalsidase alfa. Genetics in medicine : official journal of the American College of Medical Genetics. Dec 2013;15(12):983-989.
13. Schiffmann, R, Ries M, Timmons M, Flaherty JT, Brady RO. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. Feb 2006;21(2):345-354.
14. Thurberg, BL, Rennke H, Colvin RB, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney international. Dec 2002;62(6):1933-1946.

15. West, M, Nicholls K, Mehta A, et al. Agalsidase alfa and kidney dysfunction in Fabry disease. Journal of the American Society of Nephrology : JASN. May 2009;20(5):1132-1139.
16. Wilcox, WR, Banikazemi M, Guffon N, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. American journal of human genetics. Jul 2004;75(1):65-74.

ERT OPEN-LABEL EXTENSION PUBLICATIONS

1. Genzyme. A Study of the Safety and Efficacy of Fabrazyme in Patients With Fabry Disease (NCT00196716). 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT00196716?term=fabry&rank=36. Accessed August 2015.
2. Germain, DP, Waldek S, Banikazemi M, et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. Journal of the American Society of Nephrology: JASN. May 2007;18(5):1547-1557.
3. Shire. Extension Study of TKT028 Evaluating Safety and Clinical Outcomes of Replagal® in Adult Patients With Fabry Disease (NCT01124643). 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT01124643?term=Fabry&rank=76. Accessed August 2015.

Most of the 62 publications are related, as noted in Table A1. Of note, although there are 51 non-migalastat publications listed and linked in Table A1, 3 are duplicate citations that report on more than one trial (Benichou et al, 2009, Schiffman et al, 2013, and West et al, 2009) and therefore are double counted. Additionally, 4 of the 51 non-migalastat publications in Table A1 report only on quality of life (QoL) (Baehner et al, 2003, Cole et al, 2007, Watt et al, 2010, Low et al 2007). Although these 4 QoL publications do not report clinical outcomes (and are captured under HRQoL in the study listing), they are included in Table A1 because they are still linked to clinical trials and report on similar, if not the same, patient population. Therefore Table A1 contains 44 of the 62 non-migalastat publications. The 18 remaining publications are all single publication studies (Table A2).

Table A1: Related non-migalastat publications identified in the SLR

Study Type (RCT / non-RCT)	Primary Study Citation	Linked Publications	Notes for Linked Publications
Non-RCT	M. Beck, R. Ricci, U. Widmer, F. Dehout, A. G. de Lorenzo, C. Kampmann, A. Linhart, G. Sunder-Plassmann, G. Houge, U. Ramaswami, A. Gal, A. Mehta. Fabry disease: overall effects of agalsidase alfa treatment. Eur J Clin Invest. 2004; 34:838-44	P. B. Deegan, A. F. Baehner, M. A. Barba Romero, D. A. Hughes, C. Kampmann, M. Beck. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet. 2006; 43:347-52	**Observational clinical study** conducted using data from the European FOS data. Only female patients investigated. **No new data reported**
		D. Hajioff, S. Hegemann, G. Conti, M. Beck, G. Sunder-Plassmann, U. Widmer, A. Mehta, A. Keilmann. Agalsidase alpha and hearing in Fabry disease: data from the Fabry Outcome Survey. Eur J Clin Invest. 2006; 36:663-7	**Observational clinical study** conducted using European FOS data and on outcomes not of interest. **No new data reported.**
		D. A. Hughes, M. A. Barba Romero, C. E. Hollak, R. Giugliani, P. B. Deegan. Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS--the Fabry Outcome Survey. Mol Genet Metab. 2011; 103:207-14	**Observational clinical study** conducted using European and non-European FOS data and on a smaller subgroup of patients than primary publication. **No new data reported.**
		B. Hoffmann, A. Garcia de Lorenzo, A. Mehta, M. Beck, U. Widmer, R. Ricci. Effects of enzyme replacement	**Observational clinical study** conducted using European FOS data and on a

		therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). J Med Genet. 2005; 42:247-52	smaller subgroup of patients than primary publication. **No new data reported.**
		B. Hoffmann, M. Schwarz, A. Mehta, S. Keshav. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol. 2007; 5:1447-53	**Observational clinical study** conducted using European FOS data and on a smaller subgroup of patients than primary publication. **No new data reported.**
		A. Mehta, M. Beck, P. Elliott, R. Giugliani, A. Linhart, G. Sunder-Plassmann, R. Schiffmann, F. Barbey, M. Ries, J. T. Clarke. Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet. 2009; 374:1986-96	**Observational clinical study** conducted using European and non-European FOS data and on a smaller subgroup of patients than primary publication. **No new data reported.**
		A. Mehta, J. T. R. Clarke, R. Giugliani, P. Elliott, A. Linhart, M. Beck, G. Sunder-Plassmann. Natural course of Fabry disease: Changing pattern of causes of death in FOS - Fabry Outcome Survey. Journal of Medical Genetics. 2009; 46:548-552	**Observational clinical study** conducted using European and non-European FOS data. **No new data reported.**
		Beck M, Hughes, D., Kampmann, C., et al. Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: A Fabry Outcome Survey analysis. Paper presented at: Lysosomal Disease Network 2015.	**Observational clinical study** conducted using FOS data (countries not specified). **Additional data reported**
RCT	C. M. Eng, N. Guffon, W. R. Wilcox, D. P. Germain, P. Lee, S. Waldek, L. Caplan, G. E. Linthorst, R. J. Desnick. Safety and efficacy of recombinant human (alpha)-galactosidase a replacement therapy in Fabry's disease. New England Journal of Medicine. 2001; 345:9-16	D. P. Germain, S. Waldek, M. Banikazemi, D. A. Bushinsky, J. Charrow, R. J. Desnick, P. Lee, T. Loew, A. C. Vedder, R. Abichandani, W. R. Wilcox, N. Guffon. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. J Am Soc Nephrol. 2007; 18:1547-57	**OLE** of RCT
		B. L. Thurberg, H. Rennke, R. B. Colvin, S. Dikman, R. E. Gordon, A. B. Collins, R. J. Desnick, M. O'Callaghan. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int. 2002; 62:1933-46	**RCT** and OLE
		W. R. Wilcox, M. Banikazemi, N. Guffon, S. Waldek, P. Lee, G. E. Linthorst, R. J. Desnick, D. P. Germain. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet. 2004; 75:65-74	**OLE** of RCT
		B. Benichou, S. Goyal, C. Sung, A. M. Norfleet, F. O'Brien. A	**Pooled analysis** of two RCTs (Study ID 138: Eng,

		retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease. Mol Genet Metab. 2009; 96:4-12	2001 and Study ID 28: Banikazemi, 2007)
StudyID 28 RCT	M. Banikazemi, J. Bultas, S. Waldek, W. R. Wilcox, C. B. Whitley, M. McDonald, R. Finkel, S. Packman, D. G. Bichet, D. G. Warnock, R. J. Desnick. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med. 2007; 146:77-86	A. Fellgiebel, M. Gartenschlager, K. Wildberger, A. Scheurich, R. J. Desnick, K. Sims. Enzyme replacement therapy stabilized white matter lesion progression in fabry disease. Cerebrovascular Diseases. 2014; 38:448-456	**Post-hoc analysis** of RCT (NCT00074984)
		B. Benichou, S. Goyal, C. Sung, A. M. Norfleet, F. O'Brien. A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease. Mol Genet Metab. 2009; 96:4-12	**Pooled analysis** of two RCTs (Study ID 138: Eng, 2001 and Study ID 28: Banikazemi, 2007)
non-RCT	**StudyID 295:** M. Low, K. Nicholls, N. Tubridy, P. Hand, D. Velakoulis, L. Kiers, P. Mitchell, G. Becker. Neurology of Fabry disease. Intern Med J. 2007; 37:436-47	Talbot A, Nicholls, KM. Severity of Fabry Nephropathy as a Marker of Cardiovascular Outcome: 10-Year Data from an Australian Cohort on Enzyme Replacement Therapy. Paper presented at: American Society of Nephrology 2014.	**Observational clinical study** conducted in the same study centers in Australia as primary publication. **No new data**
RCT	D. A. Hughes, P. M. Elliott, J. Shah, J. Zuckerman, G. Coghlan, J. Brookes, A. B. Mehta. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart. 2008; 94:153-8	D. Hajioff, Y. Enever, R. Quiney, J. Zuckerman, K. Mackermot, A. Mehta. Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. J Inherit Metab Dis. 2003; 26:787-94	**RCT** conducted at the UK Royal Free Hospital UCL School of Medicine
		D. Hajioff, S. Goodwin, R. Quiney, J. Zuckerman, K. D. MacDermot, A. Mehta. Hearing improvement in patients with Fabry disease treated with agalsidase alfa. Acta Paediatr Suppl. 2003; 92:28-30; discussion 27	**RCT** conducted at the UK Royal Free Hospital UCL School of Medicine
		R. Schiffmann, M. Ries, D. Blankenship, K. Nicholls, A. Mehta, J. T. Clarke, R. D. Steiner, M. Beck, B. A. Barshop, W. Rhead, M. West, R. Martin, D. Amato, N. Nair, P. Huertas. Changes in plasma and urine globotriaosylceramide levels do not predict Fabry disease progression over 1 year of agalsidase alfa. Genet Med. 2013; 15:983-9	**Pooled analysis** using data from three clinical trials, including this primary publication.
		M. West, K. Nicholls, A. Mehta, J. T. Clarke, R. Steiner, M. Beck, B. A. Barshop, W. Rhead, R. Mensah, M. Ries, R. Schiffmann. Agalsidase alfa and kidney dysfunction in Fabry disease. J Am Soc Nephrol. 2009; 20:1132-9	**Pooled analysis** using data from three clinical trials, including this primary publication.
	R. Schiffmann, J. B.	R. Schiffmann, P. Hauer, B.	**RCT** evaluating same patient

RCT	Kopp, H. A. Austin, S. Sabnis, D. F. Moore, T. Weibel, J. E. Balow, R. O. Brady. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. Jama. 2001; 285:2743-9	Freeman, M. Ries, L. J. Scott, M. Polydefkis, R. O. Brady, J. C. McArthur, K. Wagner. Enzyme replacement therapy and intraepidermal innervation density in Fabry disease. Muscle Nerve. 2006; 34:53-6	population as the primary publication
		R. Schiffmann, M. K. Floeter, J. M. Dambrosia, S. Gupta, D. F. Moore, Y. Sharabi, R. K. Khurana, R. O. Brady. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. Muscle Nerve. 2003; 28:703-10	**RCT** evaluating same patient population as the primary publication
		R. Schiffmann, M. Ries, M. Timmons, J. T. Flaherty, R. O. Brady. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. Nephrol Dial Transplant. 2006; 21:345-54	**OLE** of study primary RCT
		R. Schiffmann, M. Ries, D. Blankenship, K. Nicholls, A. Mehta, J. T. Clarke, R. D. Steiner, M. Beck, B. A. Barshop, W. Rhead, M. West, R. Martin, D. Amato, N. Nair, P. Huertas. Changes in plasma and urine globotriaosylceramide levels do not predict Fabry disease progression over 1 year of agalsidase alfa. Genet Med. 2013; 15:983-9	**Pooled analysis** using data from three clinical trials, including this primary publication.
		M. West, K. Nicholls, A. Mehta, J. T. Clarke, R. Steiner, M. Beck, B. A. Barshop, W. Rhead, R. Mensah, M. Ries, R. Schiffmann. Agalsidase alfa and kidney dysfunction in Fabry disease. J Am Soc Nephrol. 2009; 20:1132-9	**Pooled analysis** using data from three clinical trials, including this primary publication.
Non-RCT	M. Lenders, N. Karabul, T. Duning, B. Schmitz, M. Schelleckes, R. Mesters, H. W. Hense, M. Beck, S. M. Brand, E. Brand. Thromboembolic events in Fabry disease and the impact of factor V Leiden. Neurology. 2015; 84:1009-16	F. Baehner, C. Kampmann, C. Whybra, E. Miebach, C. M. Wiethoff, M. Beck. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. J Inherit Metab Dis. 2003; 26:617-27	**Open-label clinical trial** recruiting patients from the Mainz hospital in Germany, a subgroup of patients in the primary publication, which evaluates patients from the Mainz hospital and the University Hospital of Munster in Germany.
		C. Whybra, E. Miebach, E. Mengel, A. Gal, K. Baron, M. Beck, C. Kampmann. A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. Genet Med. 2009; 11:441-9	**Open-label clinical trial** recruiting patients from the Mainz hospital in Germany, a subgroup of patients in the primary publication, which evaluates patients from the Mainz hospital and the University Hospital of Munster in Germany.

		M. A. Engelen, E. Brand, T. B. Baumeister, T. Marquardt, T. Duning, N. Osada, R. M. Schaefer, J. Stypmann. Effects of enzyme replacement therapy in adult patients with Fabry disease on cardiac structure and function: A retrospective cohort study of the Fabry Munster Study (FaMuS) data. BMJ Open. 2012; 2:	**Observational clinical study** of patients from the Fabry outpatient clinical of the University Hospital of Munster, a subgroup of patients in the primary publication, which evaluates patients from the Mainz hospital and the University Hospital of Munster in Germany. **No new data.**
		C. Whybra, C. Kampmann, F. Krummenauer, M. Ries, E. Mengel, E. Miebach, F. Baehner, K. Kim, M. Bajbouj, A. Schwarting, A. Gal, M. Beck. The Mainz Severity Score Index: A new instrument for quantifying the Anderson - Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clinical Genetics. 2004; 65:299-307	**Observational clinical study** of patients from the the Mainz hospital, a subgroup of patients in the primary publication, which evaluates patients from the Mainz hospital and the University Hospital of Munster in Germany. **No new data.**
		Kampmann C, Bizjajeva S, Beck M. Outcomes in Fabry disease patients after long-term agalsidase alfa enzyme replacement therapy. Presented at SSIEM Annual Meeting 2015. Abstract No. O-050. Abstract No. P-616.	**Observational clinical study** of patients from the the Mainz hospital, a subgroup of patients in the primary publication, which evaluates patients from the Mainz hospital and the University Hospital of Munster in Germany.
Non-RCT	A. L. Cole, P. J. Lee, D. A. Hughes, P. B. Deegan, S. Waldek, R. H. Lachmann. Depression in adults with Fabry disease: a common and under-diagnosed problem. J Inherit Metab Dis. 2007; 30:943-51	Hughes D, Ramaswami, U., Mckie, M., et al. Fabry disease: Impact of ERT on renal function. Single-center 5-year results. Paper presented at: Lysosomal Disease Network 2015	**Observational clinical study** of patients at the Royal Free London NHS Foundation Trust Lysosomal Storage Disorders Unit, one of the four centers evaluated in the primary publication (Lysosomal Disorders Centre at Addenbrookes Hospital, London; Lysosomal Storage Disorders Unit at The Royal Free Hospital, London; The National Hospital for Neurology and Neurosurgery at Queen Square, London; the department of Lysosomal Storage Disorders at Hope Hospital, Manchester)
		C. O'Mahony, C. Coats, M. Cardona, A. Garcia, M. Calcagnino, E. Murphy, R. Lachmann, A. Mehta, D. Hughes, P. M. Elliott. Incidence and predictors of anti-bradycardia pacing in patients with Anderson-Fabry disease. Europace. 2011; 13:1781-8	**Observational clinical study** of patientsenrolled in the same centers as the primary publication (Lysosomal Disorders Centre at Addenbrookes Hospital, London; Lysosomal Storage

			Disorders Unit at The Royal Free Hospital, London; The National Hospital for Neurology and Neurosurgery at Queen Square, London; the department of Lysosomal Storage Disorders at Hope Hospital, Manchester). **No new data**
Non-RCT	West ML, Bichet DG, Khan A, et al. Outcomes of patients over 65 in the Canadian Fabry Disease Initiative Study. Presented at ASN Kidney Week 2015. Abstract No. FR-PO166.	West M, Bichet, D., Casey, R., et al. Clinical Effects of Neutralizing Anti-agalsidase Antibodies in Patients Receiving Enzyme Replacement Therapy in the Canadian Fabry Disease Initiative Study. Paper presented at: 3rd Update on Fabry Nephropathy, 2013.	**Observational clinical study** of a subgroup of patients from the primary publication, which reports on the Canadian Fabry Disease Initiative.
		West M, Bichet, D., Casey, R., et al. Benefit of Enzyme Replacement Therapy in Fabry Disease: Comparison of Outcomes in the Canadian Fabry Disease Initiative Study. Paper presented at: 3rd Update on Fabry Nephropathy 2013.	**Observational clinical study** of a subgroup of patients from the primary publication, which reports on the Canadian Fabry Disease Initiative.
Non-RCT	Beer M, Weidemann F, Breunig F, Knoll A, Koeppe S, Machann W, et al.Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. American Journal of Cardiology 2006;97(10):1515–8.[1]	F. Breunig, F. Weidemann, J. Strotmann, A. Knoll, C. Wanner. Clinical benefit of enzyme replacement therapy in Fabry disease. Kidney Int. 2006; 69:1216-21	**Open-label, non-randomized trial** conducted at University Hospital, Wurzburg, Germany with a smaller patient population than the primary publication
		F. Weidemann, F. Breunig, M. Beer, J. Sandstede, O. Turschner, W. Voelker, G. Ertl, A. Knoll, C. Wanner, J. M. Strotmann. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. Circulation. 2003; 108:1299-301	**Open-label, non-randomized trial** conducted at University Hospital, Wurzburg, Germany with a smaller patient population than the primary publication
Non-RCT	T. Watt, A. P. Burlina, C. Cazzorla, D. Schonfeld, M. Banikazemi, R. J. Hopkin, A. M. Martins, K. Sims, D. Beitner-Johnson, F. O'Brien, U. Feldt-Rasmussen. Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. Genet Med. 2010; 12:703-12	Warnock D, Maruti, SS., Cabrera, GH., et al. Occurrence of Severe Clinical Events by Time on Enzyme Replacement Therapy with Agalsidase Beta among Patients with Fabry Disease. Paper presented at: American Society of Nephrology 2014	**Observational clinical study** using data from the Fabry Registry. **No new data.**
		Ortiz A, Cabrera, GH., Charrow, J., et al. Occurrence of severe clinical events by time on agalsidase beta among patients with Fabry disease. Paper presented at: Lysosomal Disease Network 2015	**Observational clinical study** using data from the Fabry Registry. **No new data.**
		Hopkin R, Cabrera, G., Charrow, J., et al. Risk factors for severe clinical events and the incidence of these events in male and female patients with Fabry disease treated with agalsidase beta. Paper presented at: Lysosomal Disease Network 2015.	**Observational clinical study** using data from the Fabry Registry. **No new data.**

		W. R. Wilcox, J. P. Oliveira, R. J. Hopkin, A. Ortiz, M. Banikazemi, U. Feldt-Rasmussen, K. Sims, S. Waldek, G. M. Pastores, P. Lee, C. M. Eng, L. Marodi, K. E. Stanford, F. Breunig, C. Wanner, D. G. Warnock, R. M. Lemay, D. P. Germain. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab. 2008; 93:112-28	**Observational clinical study** using data from the Fabry Registry. **No new data.**
		W. R. Wilcox, G. E. Linthorst, D. P. Germain, U. Feldt-Rasmussen, S. Waldek, S. M. Richards, D. Beitner-Johnson, M. Cizmarik, J. A. Cole, W. Kingma, D. G. Warnock. Anti-alpha-galactosidase A antibody response to agalsidase beta treatment: data from the Fabry Registry. Mol Genet Metab. 2012; 105:443-9	**Observational clinical study** using data from the Fabry Registry.

Table A2: Single publication non-migalastat studies

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Appendix 3: Reference citations for non-migalstat studies assessed in the feasibility analysis

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868 - Migalastat for treating Fabry disease [ID 868]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: Sophie Thomas

Name of your organisation: The MPS Society

Brief de*scrip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*
The MPS Society was founded in 1982 and looks after support needs of over 1200 children and adults across 25 lysosomal storage diseases and their families. It engages with health, social care and educational professionals involved in meeting the needs of our members. The MPS Society provides a support and individual advocacy service to over 500 children and adults diagnosed with Fabry disease. This is estimated to be over 70% of all those affected with Fabry disease in England.

The MPS Society has an average income of over £1.2million of which over 80% is raised through donations, fundraising, legacies and a charitable gift from the MPS Society's wholly owned subsidiary, MPS Commercial. Unrestricted educational grants from more than five pharmaceutical companies collectively did not exceed 10% of the MPS Society's annual income in y/e 31 December 2015.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- √an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee,

member, etc)

Advocacy Support Team Manager

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry

Neither I personally or the MPS Society have any links to the tobacco industry nor do I or the MPS Society receive any funding from the tobacco industry.

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Fabry disease (also known as Anderson Fabry disease) is an inherited lysosomal storage disease caused by mutations in the GLA gene which encodes the enzyme alpha-galactosidase A. Mutations in the GLA gene change the enzyme's structure and function and prevent it breaking down a fat called Gb3. Progressive Gb3 in the cells leads to a wide range of symptoms which may not appear in everyone with the disease. Progressive accumulation of Gb3 often starts in childhood and is frequently evident in adolescence.

Diagnosis

Although symptoms generally appear in childhood they usually go unrecognised until adulthood when organ system damage has already occurred. Early diagnosis is particularly important in Fabry disease as the condition is progressive and life threatening.

In England the diagnosis of Fabry disease is rarely made in children under 12 years of age unless there is an existing family history or a parent, grandparent, sibling or extended family member receives a diagnosis of Fabry disease. The largest majority of our adult members have endured decades of living with Fabry disease before being diagnosed. Premature death due to Fabry disease is prevalent in this group of patients.

Fabry disease in children

The most frequent early clinical manifestations of Fabry disease in children are neurological including acroparathesia, altered temperature sensitivity and inability to sweat. Between 60 – 80% of children report gastrointestinal symptoms including

altered bowel habits and abdominal pain. Tinnitus, vertigo, fatigue and angiokeratoma were reported in 40% of children under the age of 18 years. *Acta Paediatr 2006 Jan; 95 (1): 86 – 92 Clinical Manifestations of Children – U Ramaswami*

Some children experience major complications during their paediatric years. *Paediatr Res 2008 Nov;64 (5):550-5 Characterisation of Fabry disease in 352 patients in the Fabry Registry – Hopkin RJ et al*

Fabry disease in adults

By the time a person with Fabry disease reaches adulthood, significant build-up in GL-3 in the cells may have occurred, and new signs and symptoms related to organ damage may have occurred. From early adulthood many have developed renal disease and renal failure resulting in the need for dialysis and /or kidney transplant, cardiac disease and frequent TIAs and strokes often resulting in severe physical and mental disability and death. Hearing loss, tinnitus, the skin rash angiokeratoma, gastrointestinal problems, acroparathesia, corneal opacities, heat and cold intolerance and fatigue are the other clinical manifestations of Fabry disease that contribute to a thoroughly debilitating existence as an adult with progressive Fabry disease.

Treatment options

Until 2001 when Enzyme Replacement Therapy (Replagal & Fabrazyme) received marketing approval by the European Medicines Agency (EMA) and subsequently was approved for reimbursement in England the treatment for Fabry disease was palliative. On the licenced doses a majority of our members demonstrate significant benefit from their once a fortnight Enzyme Replacement Therapy (ERT) reporting huge reduction in fatigue and gastrointestinal symptoms. Clinically many of our young adult Fabry members believe that early access to ERT will prevent them from suffering the major organ failures suffered by previous generations of the family with Fabry disease. ERT is the only licensed approved treatment by NHS England. Whilst a once a fortnight infusion of ERT may sound invasive, for the majority of our members, it is a small price to pay to prevent further Fabry disease progression and have the opportunity to continue to live a fuller life as possible including seeing their own children grow up. Historically many patients with Fabry disease have experienced psychological difficulties which may in large be attributed to the lack of effective treatment and overwhelming burden of having to endure a lifelong (however many years that may be) multi-organ progressive disease.

The possibility of a tablet form of therapy is undoubtedly an attractive option for some patients although we sense some anxiety from Fabry patients that they need to understand better how Migalastat works, what the benefits are over either ERT and what happens if a Fabry patient moves over to oral Migalastat and feels it doesn't work as well as their ERT. A further concern is being able to be sure that the Fabry disease patient is reliable in taking the oral tablet as prescribed.

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(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

1 (ii) Fabry disease and everyday life
Fabry disease is very variable with some people showing progressive disease and others not displaying symptoms and requiring little intervention or treatment.

For many Fabry adults who were not diagnosed in childhood report very negative experiences at school including being forced to do PE and sport when they couldn't sweat and had no energy; being unable to keep up with the school academic curriculum due to fatigue, pain in hands and feet and numerous absences from school. Gastrointestinal problems were dismissed or hidden and these children were often humiliated and told they had 'growing pains'.

Whilst with a diagnosis of Fabry disease as a child current legislation provides for adaptation of the national curriculum; extra time in exams; scribes etc many children because they look no different from their peers do not want to be singled out and frequent absences from school are often unavoidable. Within the membership of the MPS Society, pro rata to the other 25 diseases we cover, significantly more children with Fabry disease are home schooled or removed from formal education than any other group. Anecdotally the evidence suggests this pattern is principally when the mother of the Fabry child (dren) also has Fabry disease and is symptomatic.

Fabry adults hold a wide range of jobs and careers but there is correlation between disease progression and reduction in hours and early retirement. The MPS Society has supported a number of members who have been discriminated against in their employment due to the employer being unwilling to make reasonable adjustment or offer flexibility to accommodate treatment or hospital visits.

For adults with Fabry disease who have experienced a delay in diagnosis, may be faced with significant organ damage, resulting in many having to face life with progressive disability usually as a result of multiple TIAs, major strokes, cardiac disease and renal failure. As a result partners, parents, siblings and children are carers or face the prospect of being a carer in relatively early life.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

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Clinicians have reported that Migalastat has shown improvements on cardiac symptoms mainly reducing LVM and has shown stabilization of Kidney function. This has been verified by at least 3 patients who are currently enrolled on the clinical trial. Clinicians have reported that Migalastat works as equally well as the other two ERT treatments. In particular this treatment could show improved benefit to those patients with cardiac involvement.

Advantages
A tablet taken every day
Quick, non-invasive, private
Less time lost from school or employment
Easier to take holidays

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

Patients have reported that improvements in mood including less mood swings and irritability were noted when they switched to Migalastat from ERT. Not having to have ERT fortnightly and the inconvenience of having to dedicate time every two weeks for this was a huge relief for patients.

Physical symptoms such as fatigue, tiredness, are still present but appear less on Migalastat. LVM has shown improvement in patients.

Mental health – mood swings are much reduced than when on ERT: there are no constraints being on the treatment; you are able to live life as near to normal and to the full; there is less impact on all areas of life.

Q of L- Patients reported that their day to day life has improved as they are not burdened with having to have fortnightly ERT and the complications and restrictions this can present, with planning holidays, impact on work, social events. Some patients felt that it enabled them to get on with life and forget that they have Fabry. One patient reported that they “felt great” as there was less impact on day to day life.

Patients reported that there was less impact on work life and time off for fortnightly infusions was not necessary. Some patients reported losing a day’s pay fortnightly while on ERT.

As Migalastat has been through the robust European Medicines Agency appraisal process to receive marketing approval Fabry patients' naïve to Migalastat are looking for an equal clinical outcome or better than that gained by current Enzyme Replacement Therapies.

3. Disadvantages
Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

Disadvantages
Patients have to be responsible for ensuring that they take their tablet as prescribed and at the same time. Some patients felt that having to remember to take another tablet was burdensome but easier than ERT. ERT cannot be forgotten whereas a tablet can.

Patients report that the impact on other family members and employment is not affected and is in fact an advantage.

At present, collection of tablets is easy as a 6 month supply is provided at clinical appointments. How easy will this be if the treatment is approved for use? Will patients pick up prescription on time and will the prescription be able to be delivered to local pharmacies for the tablets to be collected?

One patient had to come off of the treatment due to needing a pacemaker. He is now back on ERT. We are unclear whether this is one of the stop criteria for the treatment or just part of the clinical trial protocol.

One patient decided to go back on ERT as they did not get the "energy boost" when on Migalastat. However, they reported that if energy was better affected they would go back on the treatment "in a hearbeat".

The main challenge of the technology is ensuring there are fool proof measures in place to ensure Fabry patients take Migalastat at the appropriate time and do not miss doses. We see no other disadvantages to Migalastat in terms of financial impact or impact on others. We are not in a position to judge the effectiveness and impact of side effects against existing Enzyme Replacement Therapies.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

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Very few of our members have had exposure to Migalastat to have an opinion. There are currently only 10 patients on the clinical trial. All patients who shared information have spoken favourably about the technology.

Only patients with an ameanable mutation will have access to this technology.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Yes this technology is only effective in Fabry patients with an ameanable mutation.

It is estimated that there are over 700 patients with Fabry disease. The company report that approximately only 30% of patients would be eligible for this treatment. At present this treatment has only been trialled in Adults and therefore is not available to children at present.

6. Comparing the technology with alternative available treatments or technologies
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Until March 2013 the standard practice in England was Enzyme Replacement Therapy (Fabrazyme at 1mg/kg or Replagal at 0.2 mg/kg) except during the Fabrazyme shortage. However, there have been some variances in prescriptions with some patients not receiving the licensed recommendations.

Clinicians have reported that Migalastat appears to be comparable to current ERT treatments and is showing clinical benefit.

Clinicians have reported that Migalastat could be considered as a course of treatment, using the current guidelines and clinical assessment.

Patients are likely to favour a tablet that they take every other day compared to an intravenous infusion once every two weeks.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Ease of use as Migalastat is a tablet taken orally every two days and ERT is an intravenous infusion lasting 40 mins (Replagal) and 2-3 hours (Fabrazyme). The technology can be managed by the patient whereas with ERT all but a tiny minority of patients require the full or part services of a home care nurse. ERT has to be delivered every two weeks / every month through a cold store delivery van and the patient is required to be available to receive the delivery. They also need to host a pharmaceutical fridge which many patients object to and don't have room for. Fabry patients prize their confidentiality and do not want the neighbours, friends and in some cases family members knowing about their treatment.

Patients reported that not having issues with accessing veins for IV ERT was a huge benefit, no more failed attempts, pain associated with finding suitable veins and failing.

Patients report that their condition is stable on Migalastat and all have reported that LVM has improved and thickening of the heart muscle has thinned since being on Migalastat.

No patients have reported any side effects to the MPS Society in relation to taking migalastat.

One patient reported that this technology was the best form of treatment in all aspects and it had very little if no impact on family and quality of life.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We have already highlighted the need for some form of technology that reminds and ensures the patient takes Migalastat.

See scope.

7. Research evidence on patient, family or carer views of the technology
(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

No major adverse events reported by patients in contact with Society

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

Patient Reported Outcomes research
The MPS Society has carried out a PRO service on the Fabry patient treatment experience. This is appendix A

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

The key difference this technology would make is in its administration. Migalastat as an oral tablet can be taken in a matter of minutes compared with a fortnightly infusion that including preparation requires a minimum of half a day and the intrusion of cold store deliveries and hosting a pharmaceutical fridge.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

The impact of not making this technology available would be to deny a limited but significant group of Fabry patients a chance to normalise their treatment regime, reduce time off work or in education and enhance their quality of life including being able to take 2-3 week holidays without missing doses.

(iii) Are there groups of patients that have difficulties using the technology?

It is possible that some patients particularly where there are mental health issues caused by Fabry disease or through age or living alone may struggle to be compliant in taking the oral therapy as prescribed. Appropriate prompts through modern technology may reduce the risk of lack of compliance.

Other medical complications may exclude a patient from accessing this treatment (example of patient who had to come off as he needed a pacemaker and went back on ert)

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Numbers for Fabry family members known to the UK MPS Society is between 500-520

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

868 - Migalastat for treating Fabry disease [ID 868]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Migalastat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Establishing standard care dosing of Fabrazyme and Replagal in England so that if Migalastat is approved for reimbursement by NICE that the effectiveness of Migalastat can be appraised equitably based on a standard care for Fabrazyme or Replagal.

FABRY REPORTED OUTCOMES SURVEY

THE PATIENT'S EXPERIENCE OF FABRY DISEASE AND TREATMENT

357 Fabry patients on the MPS Society Registry were invited to participate in a telephone interview / written survey to provide the patient experience of Fabry disease and treatment 174 Fabry patients participated. (49% response)

The survey study was funded from MPS Society's own resources. The study was not supported in anyway by any pharmaceutical company. No patient was offered a financial incentive to participate.

Number of Fabry patient participants 174

Males 77 Females 95 Not known 2

The age of participants ranged from 3 years to 85 years
(mean 41 years)

Participants cared for by Expert Centre:

Adults (≥16 years) (N=154):

Addenbrookes Hospital, Cambridge 13
Addenbrookes/Royal Free 1 *(shared care)*
City Hospital, Belfast 14 *(includes 2 x 16 year olds)*
Belfast/Royal Free 1 *(shared care)*
Birmingham University Hospital 12
University Hospital, Cardiff 7
Great Ormond Street Hospital 2 *(2 x 16 year olds)*
National Hospital, London 16
Manchester Children's Hospital 1 (17 years old)
Royal Free Hospital 48
Salford Foundation Hospital 33 (*one 16 year old)*
Salford/Royal Free 1 *(shared care)*
Not Known 5

Children (<16 years) (N=20)
Birmingham Children's Hospital 5
University Hospital, Cardiff 1
Great Ormond Street Hospital 7
Manchester Children's Hospital 3
Royal Free Hospital 3
Not Known 1

No. on ERT 128 Fabrazyme 53 Replagal 75 No Answer 1
No. Not on ERT 41
No. Not known 3
No. on Migalastat 1

No. affected on Fabrazyme at start of shortage due to stopping treatment or dose reduction in Fabrazyme 54 :

- *My pain levels increased so much when I missed doses that I had to switch*
- *Increased pain in hands / feet. Increased fatigue, headaches and stomach cramps*
- *Increased fatigue (2)*
- *More fatigue, increased IBS, increased headaches*
- *Had 0.5 mg/kg for 6 months and felt very unwell, improved on 0.2 mg/kg of Replagal*
- *Suffered a second stroke. Consultant suggested was due to drug change*
- *Bad stomach aches, tired and fatigued*
- *Extreme fatigue, loss of strength, lower immune system, increased breathlessness*
- *Increase in GI symptoms*
- *Developed dry eye syndrome, more crises, itching, nausea, wheat intolerance*
- *Symptoms increased when my treatment went to four weekly and before I changed to Replagal*
- *Due to no treatment suffered TIAs and in Dec 2009 had a major stroke. Changed to Replagal and had major stroke in Sept 2010*
- *Pain increased and unable to work*
- *Increase in pain and GI symptoms*
- *Had TIA in Oct 2012*
- *Very tired and acroparathesia increased when not on Fabrazyme*
- *Heart condition worsened rapidly requiring bypass and valve replacement*
- *Dizzy spells, nausea, heavy body and arms*
- *Stopped sweating and felt unwell all the time*

No. switched from Fabrazyme to Replagal due to shortage 44

- *On Replagal I had anaphylactic shocks, increased fatigue and heart episodes*
- *Suffered reactions on Replagal so was put back on low dose Fabrazyme then full dose after shortage.*
- *Did not feel as well on Replagal*
- *Doctor advised I stopped Replagal as symptoms very bad so was without treatment for sometime*
- *GI symptoms improved. Raynaud's increased. LVH stopped shrinking on Replagal*
- *Had adverse reactions to Replagal. Could not start on Fabrazyme due to shortage but after reaction was changed to Fabrazyme*

No. who changed back to Fabrazyme at end of shortage 20

Are you diagnosed with LVH? Yes 73 No 66 Not Known 35

Have you had any strokes? Yes 17 No 129 Not Known 28

Have you had any TIAs? Yes…22… No…121…… NK …31……

Are you on dialysis Yes 1

Are you waiting for a kidney transplant Yes 1

Have you had a kidney transplant Yes 3

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Derralynn Hughes

Name of your organisation: Royal Free London NHS Foundation Trust
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes, I care for 300+ people with Fabry disease**.
-
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes, I am principle investigator for the UK migalastat clinical trials.**
-
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **No**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No links to the Tabacco Industry

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology? **Of 800 patients in England I would expect 50% to have amenable mutations; =400. 2/3 of these will have symptoms requiring treatment = 260 and of these 50% may elect to have the treatment ie 150.**

How is the condition currently treated in the NHS? **The condition is currently treated with intravenous enzyme replacement (agalisidase alfa or beta) given every two weeks by infusion. Not all patients require treatment. All require symptomatic care for pain, sweating abnormalities, gastrointestinal symptoms, cardiac failure, renal dysfunction and stroke**.

Is there significant geographical variation in current practice? **Practice in England has been standardised by development of clinical guidelines by the clinicians minimising geographical variation.**

Are there differences of opinion between professionals as to what current practice should be? **In England there are minimal differences in opinion on criteria for treatment. There may be some variation in around starting and stopping therapy in patients with single organ disease who reach a clinical end point.**

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? **Current alternatives to the technology include infused enzyme replacement. This has the disadvantage of requiring intra venous infusions, patients must come into hospital or have visits at home, with noisy extra refridgerator, stay in for deliveries and infusion, limit to travel, school and work. There is a risk of infusion reactions and immunogenicity which may impair clinical end points.**

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? **Fabry disease is very heterogeneous in clinical phenotypes with some severely affected early onset (classical) patients and others with later onset disease with less pain/ GI symptoms but with significant organ impairment to the heart or kidney or brain. All symptomatic patients receive enzyme replacement therapy regardless of early onset, classical or later onset phenotypes since progression significant cardiac end points for example is equivocal between groups.**

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? **Only patients with amenable mutations will benefit from the technology. Amenable mutations may result in classical or later onset phenotypes and each patient should be evaluated individually. No groups are more or less at risk from the technology.**

What is the likely impact of the technology on the delivery of the specialised service? **The impact will be to provide an oral alternative to enzyme therapy for amenable patients with benefits to patient quality of life and reduced need for funding and provision of home care.**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals? **An oral therapy will reduce requirement for home care nursing.**

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur? **Therapy is currently only provided in the context of a clinical trial.**

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
Clinical guidelines have been developed by clinicians working in the NHS England Clinicians Advisory Group (Hughes et al attached). Recent consensus guidelines have also been developed Biegstraten 2014 have not been adopted in UK although are not materially different.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use? **The technology should be easier to use in practice than ERT for patients who are amenable. Patients would require same baseline and follow up assessment of symptoms, cardiac and renal architecture and function and neurology.**

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation. **Only patients with amenable mutations as assessed via in vitro assay will benefit from the technology. The manufacturer will supply a list of amenable mutations. Other starting and stopping criteria should be the same as enzyme therapy.**

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? **The clinical trial evidence reflects clinical practice with regular monitoring of symptoms, clinical events renal function by GFR, cardiac architecture including left ventricular mass by echocardiogram. The most important outcomes were GFR and LVMSIwhich predict progression to renal failure, risks associated with reduced renal function prior to renal failure and cardiac endpoints including left ventricular failure conduction abnormalities and arrhythmias.**

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice? **There are minimal significant side effects associated with the technology**

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)? **Patients would undergo the same baseline and follow up assessments as currently. No new staff would be required. As with any new technology staff would need to be educated in its delivery but this would not involve additional resources or equipment.**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Migalastat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

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Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Katherine Peers

Name of your organisation: Queen Elizabeth Hospital in Birmingham
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?no
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? yes
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
none

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Agree with the NICE response document that states there are around 450 to 500 patients with Fabry disease.
However, looking at our own cohort of patients there are 61% who have a missense mutation, and out of that 61% only 48% are receiving treatment at the present time

How the condition is currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There are five adult centres and two paediatric centres that treat Fabry disease. The patients are expected to travel to one of these centres.
When patients attend the centres for the first time they are assessed as to whether they require treatment.
If yes, they are commenced on either Replagal or Fabrazyme which are given as infusions.
They have 1-3 treatments in hospital, and they are then discharged to home care where they receive the infusion at home.
They then attend hospital twice a year if they are receiving treatment and yearly if not.
If not on treatment then they are assessed each visit as to whether they require treatment.
If the current centres remain then patients will still be required to travel to one of the centres to monitor the Fabry disease. However, the advantage of this therapy is that they will not be required to have two weekly infusions which take one to three hours. The disadvantage of treatment is that they will need to remember to take the medication daily and there may be compliance issues.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
Male patients with classical Fabry disease have a poorer prognosis than those with the cardiac variant. Both groups have their share of missense mutations.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?
The present system of giving infusions at home would be obsolete for the patients who commence this therapy. This means there may be fewer staff required to give infusions at home.
However, there may need to be consideration regarding the monitoring of compliance with the therapy.

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Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what
This technology is not yet available.
Infusions are usually given according to the licence, although this may vary between centres.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

We are waiting for new guidelines regarding Fabry disease to be implemented. Currently patients on infusions undergo cardiac and renal assessment yearly.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
The advantage of this new therapy is that it is oral so is more convenient for the patients and easier than having infusions every two weeks

There need to be strict starting and stopping criteria to ensure that patients who are benefitting remain on treatment. If patients are deteriorating it could either be a sign of non-compliance or that the medication is not working for them, in which case the patient will need to be counselled.

There could be issues relating to compliance as the patients are not seeing immediate benefits from taking the medication, making it difficult to remember to take the tablets.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
Both medical and nursing and pharmacy staff are capable of educating patients about medication and counselling them regarding compliance, other than written education regarding the particular drug there should be no need for technology or additional education to start using this medication.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Migalastat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

As it is easier for a patient to take oral therapy than receive an infusion it is unlikely that this would discriminate against any group of patients having oral therapy.

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Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease [ID 868]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Dr Ana Jovanovic

Name of your organisation

Salford Royal NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **Yes, Consultant Metabolic Physician**
-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Fabry disease is a lysosomal storage disorder associated with accumulation of globotriaosylceramide (GL-3) as a result of alpha galactosidase deficiency. Enzyme replacement therapy is the only available disease modifying treatment. Two enzyme formulations are licensed for treatment of Fabry disease: agalsidase alfa (Replagal™, Shire HGT) at a dose of 0.2mg/kg intravenously every two weeks and agalsidase beta (Fabrazyme™, Sanofi Genzyme) at a dose of 1mg/kg intravenously every two weeks.

Is there significant geographical variation in current practice?
No

Are there differences of opinion between professionals as to what current practice should be?
In England we have a nationally agreed guideline that represents the current practice

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Yes. Enzyme replacement therapy (ERT) has been available for more than 10 years. Two enzyme formulations are licensed for treatment in Fabry disease.

Advantages:

First available disease modifying therapy that replaces enzyme deficiency
More than 10 years of experience of using ERT
Registry data on clinical outcomes, clinical studies and clinical trials results have been published.
ERT has been shown to slow the progression of renal impairment and cardiomyopathy. Treatment also appeared to delay the onset of morbidity and mortality. (Beck M. Mol Genet Metab Rep. 2015 Mar 5;3:21-7)
Eighty-one per cent of adult patients with classic Fabry disease receiving agalsidase beta treatment for a median of 10 years remained free of severe clinical events and 94% of patients were alive. (Germain D. J Med Genet. 2015 May;52(5):353-8)

Disadvantages:

Intravenous infusions delivered every 2 weeks
High burden of treatment
Risk of the infusion reactions and complications associated with exogenous protein administration
High cost associated with ERT administration in hospital or at home

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Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
There is a poor genotype phenotype correlation and there is little evidence that genotype predicts outcome

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Migalastat is effective only in patients with amenable mutations and residual enzyme activity
From experience with enzyme replacement therapy, early treatment is likely to be more effective than treatment in more advanced disease.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

There is already a well-established system for assessment and treatment of patients with lysosomal storage diseases including Fabry disease. Under the highly-specialised framework five adult and three paediatric centres have been commissioned in England. These centres provide multidisciplinary care for patients with Fabry disease and other lysosomal storage disorders. It is therefore expected that Migalastat will be provided by the existing centres.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

There are several patients receiving therapy as part of the clinical trial programme.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Guidelines for treatment of Fabry disease with enzyme replacement therapy have been developed. However, no specific guidelines exist on use of chaperone therapy in Fabry disease

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Migalastat chaperones endogenous alpha galactosidase to lysosomes where the enzyme activity is restored only in patients with amenable mutations.
Migalastat stabilises renal function and improves cardiac function in patients with amenable mutations.
The technology will be easier to use and the treatment burden will be lower
Risk of infusion related reactions and complications associated with exogenous protein administration will be removed.
Oral therapy will be more convenient and easier to administer than the current biweekly infusions with enzyme replacement therapy
The patients will receive and self-administer therapy at home. There will be no need to commence the technology in hospital.
There will be no need for homecare arrangements to deliver the technology
Genetic testing will be required.

Patients should have regular monitoring 6 monthly to annually.

Recommended Investigations for patients with Fabry disease

General:
1. Medical history and family pedigree 2. Clinical examination 3. Vital signs 4. Pain score (BPI) 5. Age appropriate Quality of Life score (SF-36 or EQ5D)
Cardiac:
1.ECG 2. 24 hour ECG 3. Echocardiogram
Renal:
1. Glomerular Filtration Rate: Cr51 EDTA OR estimated GFR (mdrd). 2. Spot urine Alb/Creatinine ratio or protein/Creatinine ratio 3.Renal biopsy- at the discretion of the renal physician
Neurology
T2 weighted MRI brain examination (CT if MRI precluded by pacemaker etc).
Audiology: 1. Pure tone audiogram or age appropriate hearing assessments
Laboratory Investigations:

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1. Full blood count 2. Urea & electrolytes and creatinine 3. Liver function tests 4. Fasting lipid profile (not in children) 5. Plasma lyso Gb3

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Consensus guidelines will address starting and stopping criteria. Amenable mutation must be identified.
Current starting criteria for enzyme replacement therapy in England
Evidence of cardiac disease
Evidence of renal disease
Evidence of Neurovascular disease -Previous stroke or TIA in the absence of other risk factors
Neuropathic pains
Gastrointestinal symptoms such as pain, vomiting or altered bowel habit which are significantly reducing quality of life and not attributable to other pathology.

Current stopping criteria for enzyme replacement therapy in England
Intolerable and unavoidable adverse effects.
Intercurrent illness, where either long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for Fabry disease.
At the request of the patient, or properly allocated guardian acting in the patient's best interests, if the patient is properly deemed not competent.
If the circumstances of the patient's lifestyle are such that sufficient compliance with treatment is not possible.
Objective evidence of disease progression in measured clinical criteria which are not (1) Attributable to a secondary pathology (2) Commensurate with natural age-related decline (3) Remediable by changing product or institution of other simple therapeutic measure.
If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The trials were conducted in the UK

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Surrogate outcomes were employed indicating reduction in renal GL-3 deposition, decrease in plasma lyso-Gb3 and reduction in left ventricular mass index. There was an improvement in gastrointestinal symptoms. These outcomes on well- established surrogate markers, indicate an impact on renal and cardiac disease progression. To date, there is no evidence to address long term clinical endpoints progression to the end stage renal disease,

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cardiovascular events, strokes and deaths. Planned registry studies should establish long term impact in clinical practice.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The frequency and distribution of adverse events were similar in placebo and Migalastat treated group

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No additional information known.

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Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There is already a well-established system for assessment and treatment of patients with lysosomal storage diseases including Fabry disease. Under the highly-specialised framework five adult and three paediatric centres have been commissioned in England. These centres provide multidisciplinary care for patients with Fabry disease and other lysosomal storage disorders. It is therefore expected that Migalastat will be provided by the existing centres.

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More patients may be identified and this can increase the need for NHS resources. Disease awareness has increased in the recent years.

Equality and Diversity

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- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which migalastat is/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts

No such impacts are known.

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Migalastat for treating Fabry disease

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name:Professor Atul Mehta

Name of your organisation Lysosomal Storgae Disorders Unit, Royal Free Hospital London UK

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? No
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

See below
Is there significant geographical variation in current practice?
No – standardised across the UK
Are there differences of opinion between professionals as to what current practice should be? Not significantly; some issues around dose of ERT
What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Enzyme Replacement therapy (ERT). 2 formulations, both equally effective. Modestly effective but only stabilises, does not reverse, disease manifestations. Excellent supportive care id mandatory.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Although the condition is X linked, females often symptomatic and often need treatment. Patients with the late onset forms progress more slowly than patents with 'null' mutations.
Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? Only selected patients with missense mutations will benefit from Migalastat

What is the likely impact of the technology on the delivery of the specialised service?
Migalastat is oral; ERT has to be injected, so there may be a cost saving. Patients should still attend a specialist centre for review every 6 months. Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?
Unlikely

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Migalastat is not yet available – only trials

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Currently, patients considered to have Fabry disease are referred to one of the UK Specialist LSD centres for diagnostic and clinical evaluation. These centres are in London (Royal Free, UCH (National Hospital for Nervous diseases), Great Ormond Street), Birmingham, Manchester (Salford) and Cambridge (Addenbrookes). The diagnosis must be confirmed by enzyme assay and DNA analysis for the genetic mutation. Subjects who have Fabry disease are then assessed to see if they have evidence of clinical disease and whether they fulfil criteria for treatment with enzyme replacement therapy. The Treatment guidelines have been formulated by the clinical

advisory group, who are the consultants at the UK centres, with support from patient group representatives. They are available on the UK NHS England LSD Centres website as a SOP. The European Fabry Expert Group is a group of independent experts in Europe who have also formulated Guidelines for starting and stopping enzyme replacement treatment in Fabry (Biegstraten et al Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document Orphanet Journal of Rare Diseases201510:36). The UK is well represented in this group, and patient organisations have contributed to the document.
The evidence underpinning the guideline is discussed in the paper. There is a paucity of Grade 1 evidence in the field of rare disease generally; there is Grade 2 evidence from clinical trials and observational studies. Many of the studies have been sponsored by the manufacturers of the 2 enzyme preparations, agalasidase alfa (Shire) and agalsidase beta (Sanofi-Genzyme).

Patients with classical Fabry disease have a genetic mutation which causes complete loss of function 9'null mutations'). These individuals are not candidates for the new technology, migalastat. Many individuals have missense mutations in the gene which encode enzyme which has reduced activity. Some of these subjects present with a late onset from of the disease, which often predominantly only affects a single organ (eg the heart or the kidney).

Migalastat is a small molecule chaperone therapy which may have a role in the treatment of these subjects with late onset Fabry disease, due to a missense mutation. Perhaps 50% or so of the mutations identified in these patients are amenable to the chaperone and the treatment may be of value to perhaps 30 - 50% or so of the total number of patients being treated with enzyme replacement in the UK. We think there may be 600 or so Fabry patients receiving ERT in the UK

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Easier to use as it is oral; but no other real differences.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
European Guidelines cover these areas. The additional testing is the DNA analysis – but this is done across the UK anyway. An in vitro assay to see if migalastat increases enzyme activity in cells from individual patients has been used in some of the trials and could be considered.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.

Yes it does

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
Tissue biopsy – eg renal biopsy – may not be feasible in clinical practice
What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Generally well tolerated

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The relevant sources are all available in published works; the manufacturers will have additional data

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Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Migalastat could be implemented quite easily within the pathway that exists in the UK for these patients.

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which migalastat is/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts

You should have patient group representation. Patients with rare diseases require drugs covered under the orphan drugs regulations and such subjects should not be disadvantaged. There are legitimate reasons for a price differential between orphan and non-orphan drugs

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868 - Migalastat for treating Fabry disease [ID 868]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: Leslie Hilliard

Name of your organisation: N/A

Brief de*scrip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

N/A

Are you (tick all that apply):

- ✓a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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868 - Migalastat for treating Fabry disease [ID 868]

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

I was diagnosed in 2005 at the age of 56years but had experienced symptoms since the age of 5 years, which was mainly stomach pain and diarrhoea and severe pain in my feet.

During my teenage years I had very severe pain in my feet, had excessive sweating and severe stomach cramps and constant diarrhoea. I had very low energy levels.

In my 40's my pain started to increase in my feet and there were times when I struggled to walk as it felt like I was walking on hot coals.
I went to the doctor on numerous occasions over the years but did not get any diagnosis.

In 2005 my sister, who is one of 10 children, was seen by a heart consultant in London with angina and he suspected Fabry and she got the confirmation and I was tested and diagnosed in 2005 and I was found to have thickening of the heart valve

The diagnosis came as a huge shock to me and my family, our immediate concern was for my three daughters who we knew would be a carriers. I had a huge amount of guilt of knowing that I had passed this to my daughters. Although I was glad that I finally had an answer and a reason for my symptoms, I only wish that it was picked up when I was younger as more of my family may have had a better outcome if they had been monitored and started treatment when it first came out. I sadly have lost brothers and sisters to Fabry and at least 6 out of the 10 of us have it.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing

- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

The disease has had an impact on all areas of everyday life on my physical and emotional wellbeing. It is only now after being on treatment that I am able to participate and enjoy taking part in activities and getting some resemblance of my life back.
Reflecting back on my childhood I struggled to take part in sports and was classed as lazy.

Since leaving school, I worked full time, taking little time off due to sickness and was able to undertake all duties of my job role.

Physical Impact
Before treatment I suffered from very severe pain in my feet and joints, I had severe sweating, extreme fatigue, breathlessness and gastro intestinal issues which would be from stomach cramps to chronic diarrhoea.

I have always been an active person who had a physical job and a can do attitude. Not being able to do simple things and taking part in family activities were every day struggles.

Emotional wellbeing
Going from a person who was physically active to someone who struggled to participate in anything including everyday tasks was hugely burdensome. I feel that I missed a large part of my girls childhood as I did not want to go out and take them out to the zoo or the park as I was in pain, breathless and fatigued. Family holidays which should have been a pleasure were a nightmare for all my family as the heat would increase my pain levels and fatigue and I would become aggressive and moody. I had to give up playing golf as I could not do the whole course due to fatigue. Slowly my family and social life began to diminish.

Everyday life
My life changed in all aspects. The constant pain, low energy levels, lack of stamina, inability to carry out simple tasks. I went from being an active person with good social life and family to someone who rarely went out and if I did it was only for a short time before I had to return home due to exhaustion.
Tasks around the home such as decorating would be extremely hard to do and this would cause friction between myself and my wife as everything took me so much longer. Frustration and anger became part of my life which was upsetting to me as I did not understand why I felt the way I did.

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868 - Migalastat for treating Fabry disease [ID 868]

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

Having enrolled on the clinical trial in June 2006 this has been a lifeline to me. Not only do I feel physically better, I have increased energy. My reported outcomes indicate that my thickened heart muscle has gone back to normal. My mental health has improved enormously. Although I am getting older I have never felt better in my life.
My stomach problems have ceased and I do not have the pain in my body and feet.
My excessive sweating has stopped and I can now spend hours fishing in hot sunshine without causing any issues
I am able to take part in all aspects of family life.
I can now go on holiday without having to worry about coming back and having to have treatment if I took ERT.
I can work full time and not take time off work to have ERT. I do not have the constraints of having to have a storage fridge or delivery issues if I was on ERT.
I go up to my specialist centre once every six months for tests and pick up my 6 months supply of medication at the same time.

My Family and work colleagues have seen such a difference in my wellbeing and I am able to do all the things that held me back before and that includes the decorating.
I feel as though I am starting my life over and want to make up for the time I lost feeling so unwell, and enjoy life with my family and friends.

3. Disadvantages
Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

I view the technology as positive and if your disease is significant enough to meet the requirements of treatment, I would encourage anyone to have it. There are no negatives from my perspective.

I have tolerated the new technology well with no side effects.
When I first started the treatment I had to change the pattern of my work due to increased appointments but this does not affect now as I can book time off when I go for my six month check.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

It is my experience that all those receiving treatment have a positive view on the effects and usefulness of the treatment

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Everyone should be clinically assessed and an individual recommendation for treatment made if their presenting symptoms meet the criteria for treatment. I understand that some patients may not require treatment but should be monitored closely and treatment reviewed if symptoms deteriorate.

6. Comparing the technology with alternative available treatments or technologies
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

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868 - Migalastat for treating Fabry disease [ID 868]

(i) Please list current standard practice (alternatives if any) used in the UK.

Enzyme Replacement Therapy

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

The technology improves the symptoms of the condition, has reduced my heart condition and has increased my energy levels, alleviated the pain and stomach problems and my mental health could not be better.

Taking a tablet rather than enzyme replacement therapy has the advantages of managing your treatment yourself, not being constrained to taking time out of your routine to have treatment. Being able to go away for long periods of time, in this country and abroad, without the worry of not having the treatment or having to try and arrange it.
Not having the potential problems of trying to get access to a vein for treatment if you have been on ERT for years, alleviating the need to have a portacath
No storage issues. Not having to have a specialised fridge to store the ERT or having to be available to wait for the delivery.

Young people would find this technology easier to manage and less intrusive on their life.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

There may be a reluctance to move from ERT to new technology if patients have been on ERT for many years they may have concerns over the efficiency.

The new technology may need visits to the specialist centre to be more frequent

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions.

Not aware

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

Not aware

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868 - Migalastat for treating Fabry disease [ID 868]

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Improved Health my heart cardiac condition is rectified.
My daughter may have been reluctant to have ERT due to the inconvenience but she uses this technology so that has given me peace of mind
Better quality of life being able to work and go on holiday for longer periods of time without the constraint of ERT.
Ease of use taking a tablet rather than enzyme replacement therapy.
Managing your treatment yourself, not being constrained to taking time out of your routine to have treatment.
Not having the potential problems of trying to get access to a vein for treatment if you have been on ERT for years, alleviating the need to have a portacath.
No storage issues. Not having to have a specialised fridge to store the ERT or having to be available to wait for the delivery.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

Poor Quality of Life
Risk of deteriorating health
Premature Death
Potentially more younger sufferers may rebel and stop taking treatment if they have to be on ERT

(iii) Are there groups of patients that have difficulties using the technology?

N/A

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

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868 - Migalastat for treating Fabry disease [ID 868]

Equality
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- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Fabry is a hidden disease and just because someone may outwardly present as being fine, the inside and the affects of the disease is a different story

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Migalastat for Fabry disease

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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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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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.

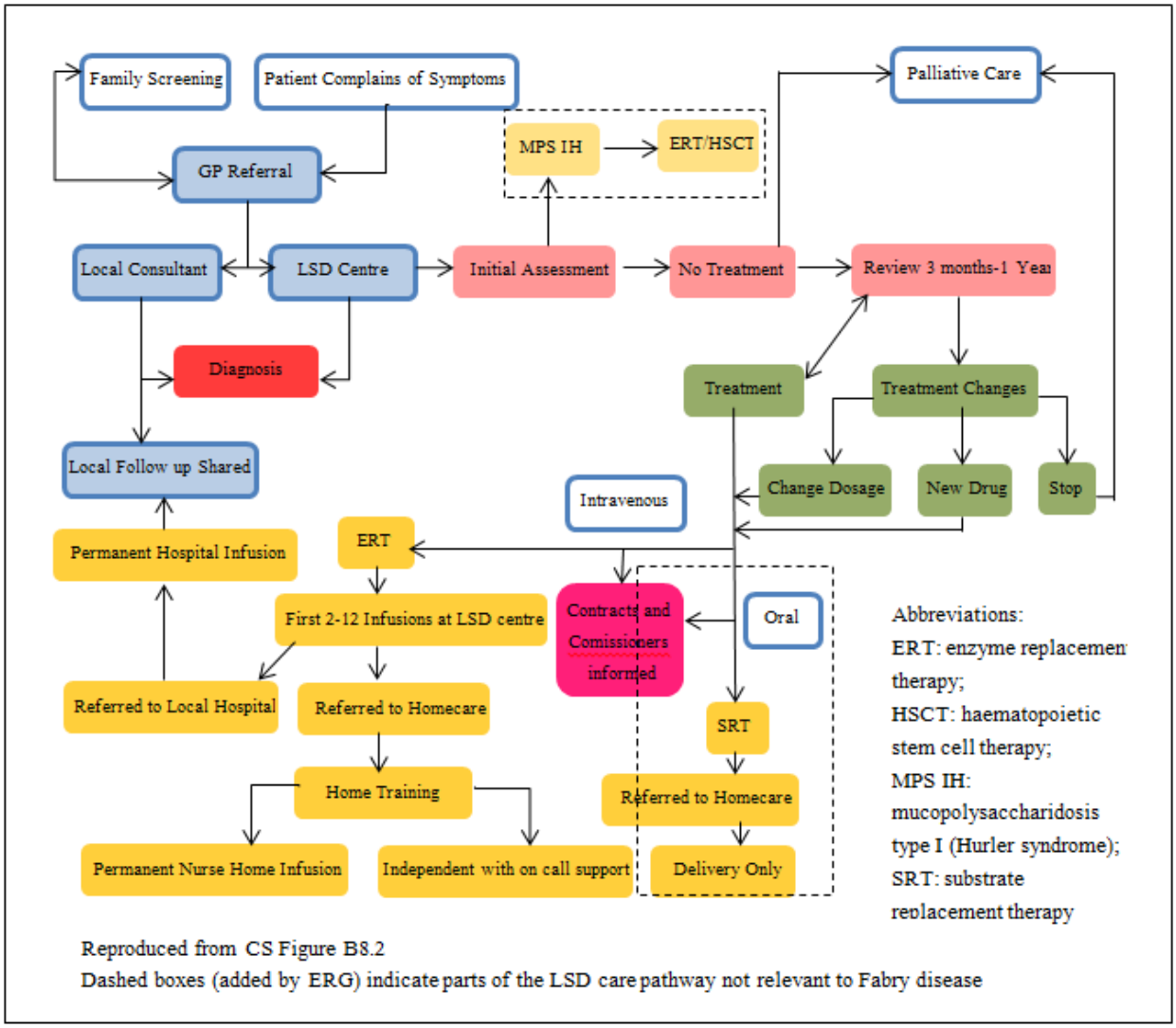

Figure 1 NHS England care pathway for the paediatric LSD Service

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.

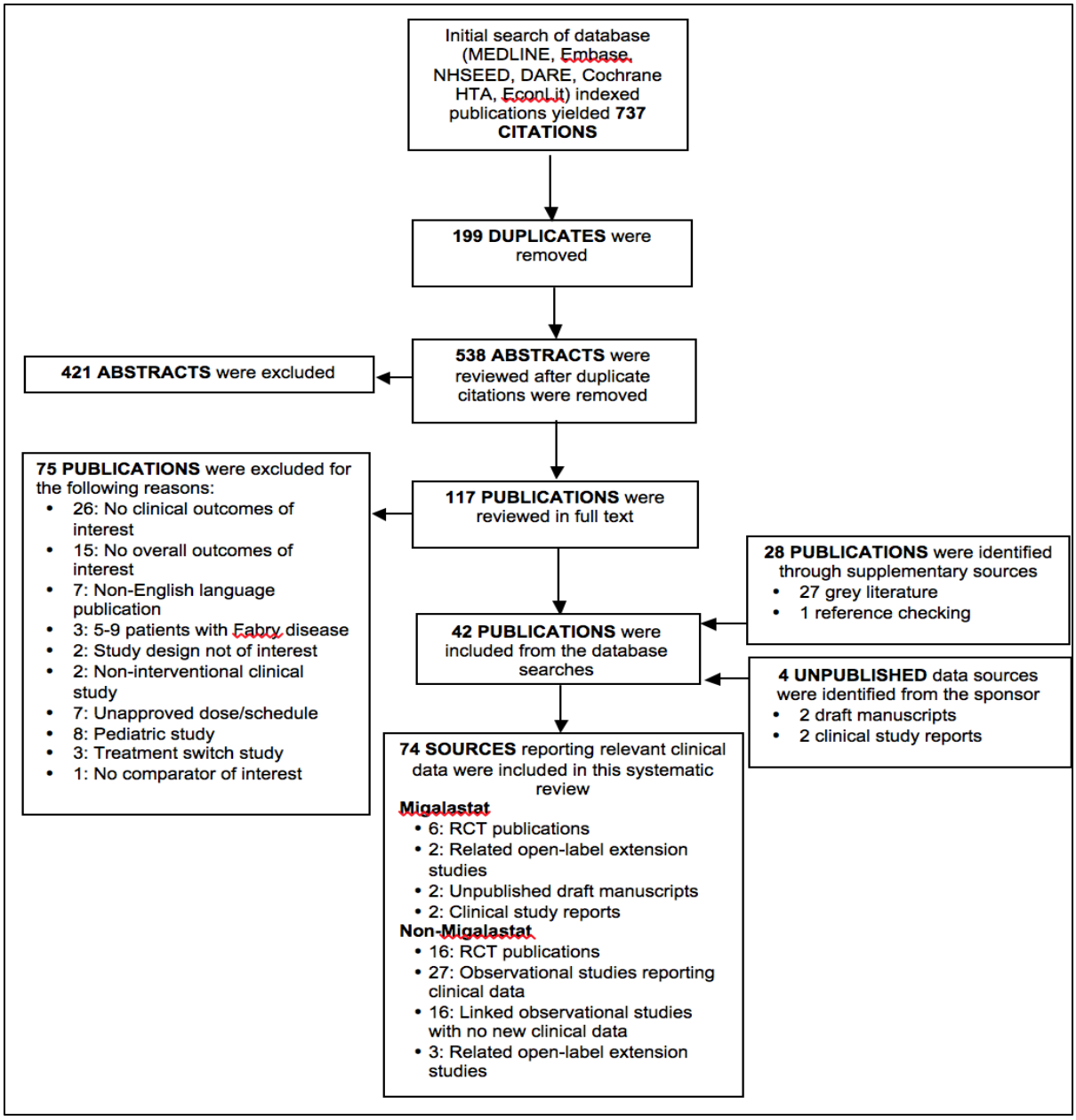

Figure 2 Study selection flow chart for the company's review of clinical effectiveness

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 ($eGFR_{CKD-EPI}$) 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

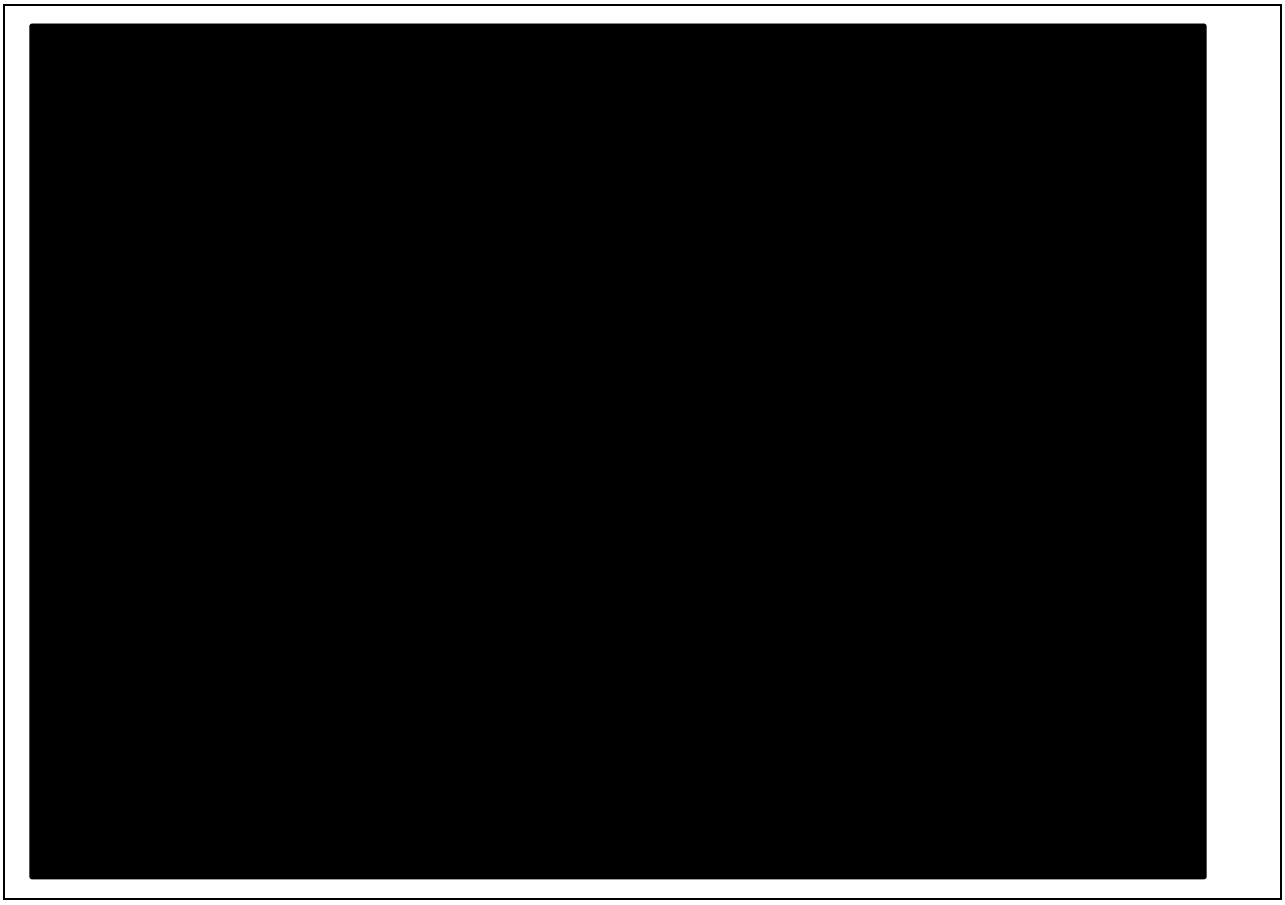

Figure 4 CONSORT flow chart for the FACETS RCT and OLE studies

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 Agalsidase beta Unspecified	[redacted][a] [redacted][a] NR	[redacted] [redacted] NR	 NR NR 5 (15)	 NR NR 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~~).

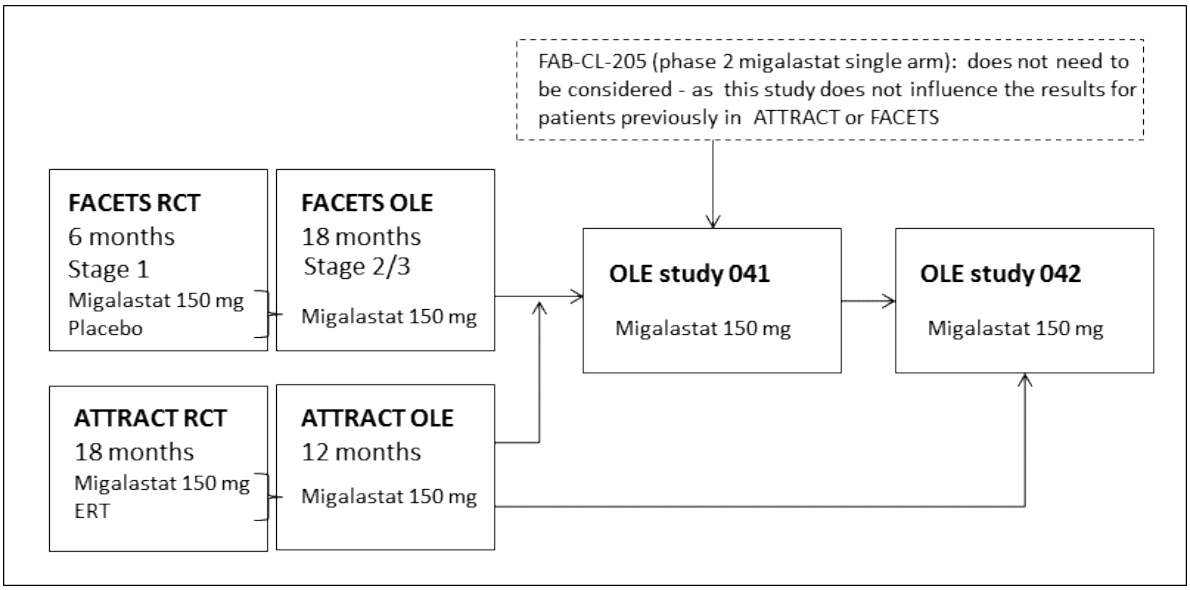

Figure 5 Summary of the relationship between the ATTRACT, FACETS and OLE studies

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 3.3~~3.3~~).

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 $eGFR_{CKD\text{-}EPI}$ 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 $eGFR_{CKD-EPI}$) 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 $eGFR_{CKD-EPI}$ outcomes (CS Table C9.14). However, this does not apply to the [redacted] analysis of $eGFR_{CKD-EPI}$ 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.

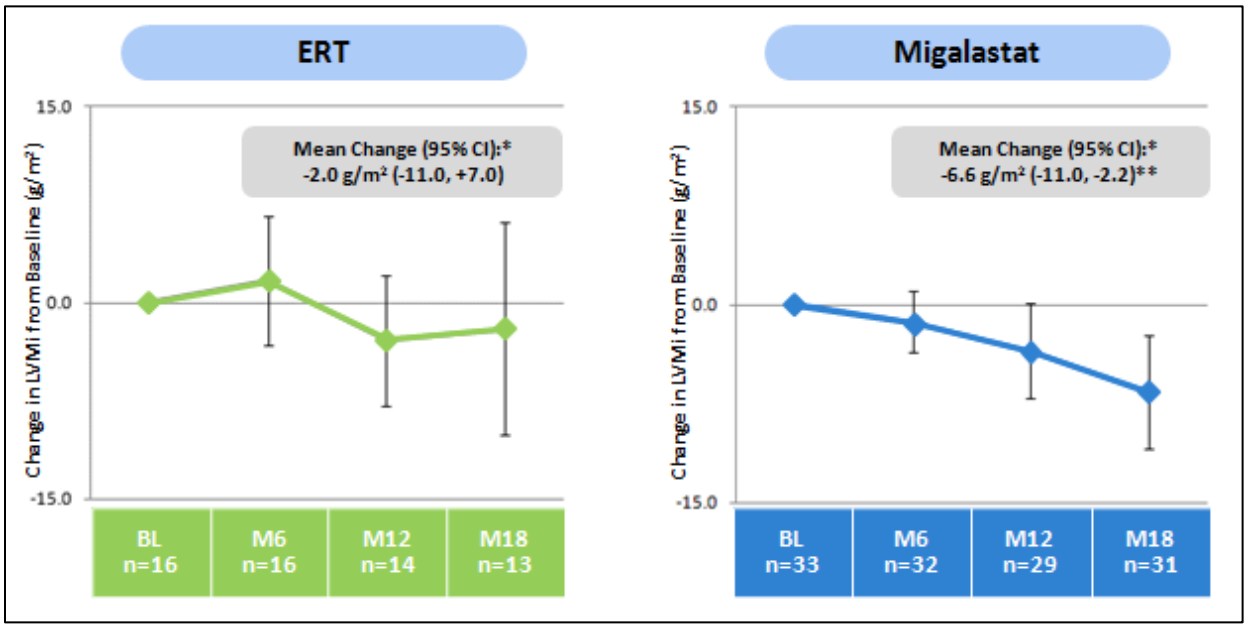

Figure 7 Left ventricular mass index change in the ATTRACT trial

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 $eGFR_{CKD\text{-}EPI}$ 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)
$eGFR_{CKD\text{-}EPI,}$ 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 ($eGFR_{CKD\text{-}EPI}$) 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 3.1.7~~3.1.7~~), 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 22~~Table 22~~), the FACETS trial (Table 23~~Table 23~~) and also the OLE studies following the FACETS trial (Table 24~~Table 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 3.1.1~~3.1.1~~ 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.

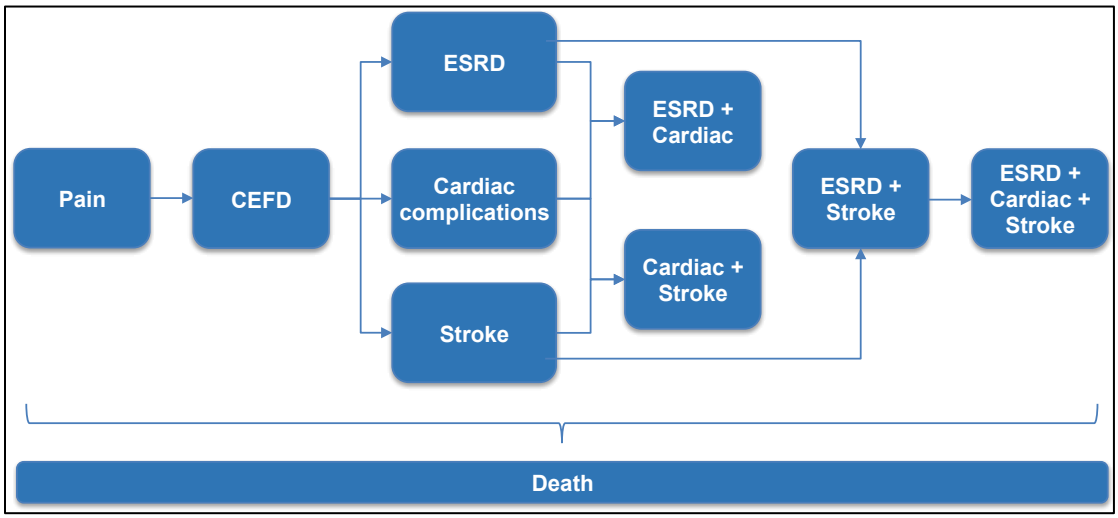

Figure 8 Company model schematic (CS Figure D12.1)

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 4.4~~4.4~~), 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 31Table 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 4.4~~4.4~~).

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.

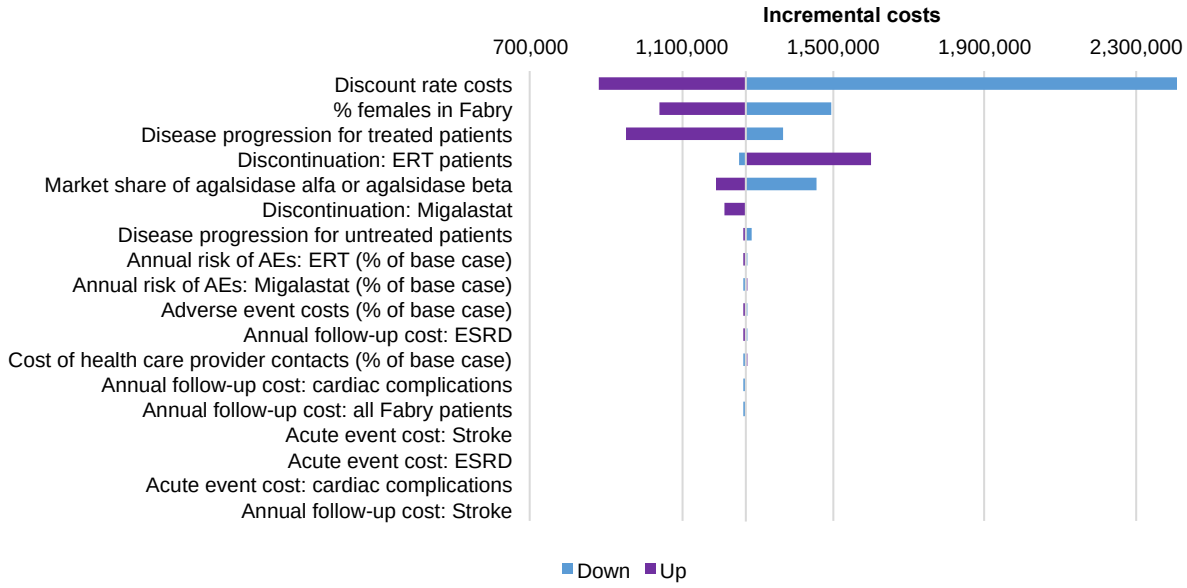

Figure 9 Tornado diagram illustrating cost differences in company one-way sensitivity analyses (CS Figure 12.7)

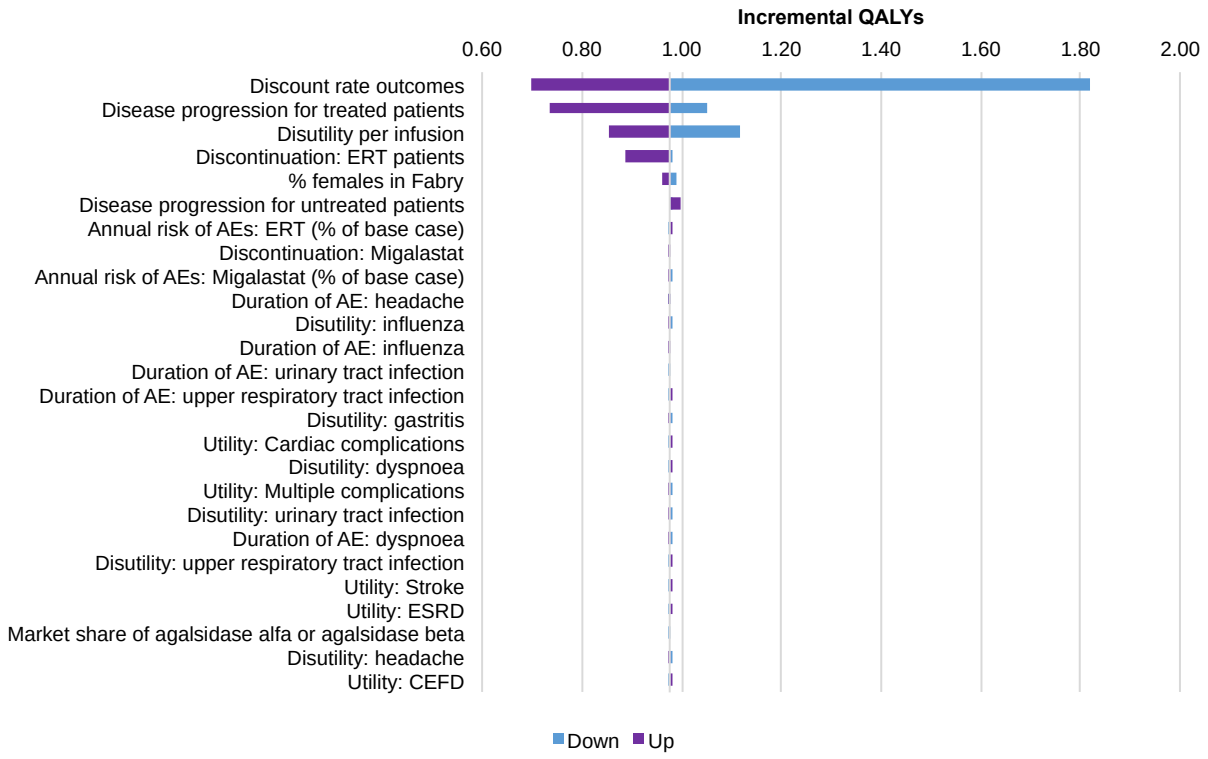

Figure 10 Tornado diagram illustrating QALY differences in company one-way sensitivity analyses (CS Figure 12.6, p219)

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 4.3.6~~4.3.6~~)

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 4.3.8~~4.3.8~~).
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 4.3.8~~4.3.8~~).
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 4.3.9~~4.3.9~~).
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 4.3.6~~4.3.6~~).
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 4.3.6~~4.3.6~~).
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 4.3.3~~4.3.3~~, 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 4.3.6~~4.3.6~~ 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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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Migalastat for treating Fabry disease [ID 868]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Thursday 2 June 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Contents

Issue 1 Statements reflecting on comparable efficacy of migalastat and ERT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG has questioned the evidence demonstrating comparable efficacy of migalastat and ERT in patients with Fabry disease. Page 13: "*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.* Page 18: "*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*" Page 82: "*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*	Delete the following sentences: Page 13: *"Changes in biochemical outcomes reported in ATTRACT show a pattern of non inferiority between migalastat and ERT, except that activity of the target enzyme α-galactosidase A in white blood cells increased in the migalastat group but not the ERT group."* Page 18 "*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*." Page 82 "*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*	Amicus are strongly of the opinion that it is beyond the remit of the ERG to make judgemental interpretations and statements on the evidence provided in the submission. The ERG's assertions are also in conflict with the opinion of the Committee for Medicinal Products for Human Use (CHMP). Migalastat underwent thorough examination by the CHMP who recommended approval and agreed that data from ATTRACT was sufficient to demonstrate a treatment effect comparable to ERT over 18-months (EPAR): • "The applicant demonstrated that migalastat was comparable to ERT in maintaining stabilisation of eGFR. • The effect on LVMi after 18 months, was comparable in both migalastat and ERT groups. The mean effect on LVMi was maintained in both naïve (study 011) and ERT pre-treated patients after 24, 30 and 36 months of treatment. • As indicated in the scientific advice by the CHMP (EMEA/CHMP/SAWP/288057/2009), the analysis of the composite clinical outcome endpoint - indicated comparable effects in kidney and heart between migalastat and ERT groups. • Comparable effects were observed on lyso-Gb3 and LVMi between ERT and migalastat treated	ERG page 13: Not a factual inaccuracy. However, the ERG agrees that the statement does not fully convey the point that plasma lyso-Gb3 concentrations remained low and changes in both groups were not significantly different from zero (ERG Table 15). Text has been amended for clarity: added to erratum (page 13) ERG pages 18, 128 and 140: Not a factual inaccuracy. The statement that the trial was not large enough to demonstrate superiority or non-inferiority to ERT is correct. The statistical approach agreed between the company and EMA was post hoc and a pragmatic way of establishing 'comparability' of migalastat and ERT in a rare disease population, but this should not be confused with unequivocal demonstration of equivalence, non-inferiority or superiority. The ERG has clearly reported the company's approach in ERG report section 3.1.6.2. ERG page 82: Not a factual inaccuracy. This statement reflects

provides an unbiased estimate of the clinical equivalence of migalastat and ERT" Page 124: *"We produced this threshold analysis because the data on migalastat's efficacy compared to ERT are highly uncertain."* Page 128: *"The ERG considers that the ATTRACT trial was not sufficiently powered to demonstrate clinical equivalence between migalastat and ERT"* Page 140: *"There is limited evidence from the company's clinical trial to support clinical equivalence."*	*migalastat and ERT*" Page 124: *"We produced this threshold analysis because we believe the data on migalastat's efficacy compared to ERT are highly uncertain."* Page 128: *"The ERG considers that the ATTRACT trial was not sufficiently powered to demonstrate clinical equivalence between migalastat and ERT"* Page 138: *"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."*	groups" Based on the actual observed 012 data, the minimum difference in GFR that the study was able to detect based on the comparability criteria was 0.71 ml/min/1.73m^2/yr for eGFR and 1.24 ml/min/1.73m^2/yr for mGFR. Given the decline in GFR in untreated Fabry patients of -2 to -12 ml/min/1.73m^2/yr, these detectable differences are acceptable and meaningful. Importantly, the final eGFR/mGFR data strongly support comparability and far exceed the pre-specified comparability criteria: eGFR point estimate +0.6 (mean), -0.4 (median), complete overlap of 95% CIs; mGFR point estimate -1.1 (mean), +0.3 (median), complete overlap of 95% CIs. Additionally comparability of these co-primary endpoints were supported by comparability in key secondary outcomes of LVMi, and clinical composite events that numerically favoured migalastat. Finally, the data shows a clear pattern that, in terms of biochemical outcomes, migalastat is non-inferior to ERT in controlling biochemical markers.	uncertainty around the key outcomes (wide confidence intervals) together with concerns about trial rigour (including uncertainty around the randomisation and allocation procedures unresolved despite a clarification request, imbalance in the study group demographic characteristics, and unbalanced attrition). ERG page 124: Not a factual inaccuracy, merely an explanation for this threshold analysis. ERG page 138: Not a factual inaccuracy. The ERG statement accurately reflects that there is uncertainty around the GFR results, both within and across the different GFR measures. We note that the migalastat EPAR considers the ATTRACT study groups to be well balanced demographically, cf ERG report section 3.1.3.3. The EPAR did not report risks of bias.

Issue 2 Justification of the non-inferiority study design and primary endpoint comparability criteria in ATTRACT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11: "*The company aimed to*	Please delete the following	This is inaccurate. As stated in the CS, page 80 "*A*	Not a factual inaccuracy.

demonstrate non-inferiority of migalastat compared to ERT for the measured glomerular filtration rate (mGFR) and estimated GFR (eGFR) outcomes, but the total number of patients randomised (n=60) was inadequate for a non-inferiority analysis. The company instead made an assumption that migalastat has 'comparable' effectiveness to ERT according to two criteria: differences between migalastat and ERT groups in annualised changes in mGFR and eGFR were within a pre-specified limit of 2.2 mL/min/1.73m^2; 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."* Page 57: "*As acknowledged in the CS, due to small sample*	sentence: "The company aimed to demonstrate non-inferiority of migalastat compared to ERT for the measured glomerular filtration rate (mGFR) and estimated GFR (eGFR) outcomes, but the total number of patients randomised (n=60) was inadequate for a non-inferiority analysis." And replace with: "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/1.73m^2; and confidence intervals for the mean change in these	*standard non-inferiority analysis comparing migalastat and ERT on the co-primary endpoints was not possible due to the small sample size*." The ERG did not request this information during clarification questions, when we would have been able to provide a comprehensive response. Based on scientific advice in 2008/2009, the 012 study was designed as a descriptive comparison between migalastat and ERT with mGFR as primary endpoint. The protocol was finalized using criteria of >50% overlap of 95% CIs as a descriptive comparison of comparability between the 2 groups. After reviewing eGFR and mGFR results in study 011 in 2014, scientific advice was initiated to propose elevating eGFR as a co-primary endpoint based on higher than anticipated variability in mGFR in study 011. Based on input from this scientific advice, the final 012 primary analysis was specified as a descriptive comparison of comparability with criteria of >50% overlap of 95% CIs plus the point estimate of the mean change being less than <2.2 ml/min/1.73m^2/yr for both eGFR and mGFR. The use of these 2 criteria together provides a comparability comparison that is similar to a traditional non-inferiority analysis, but that is more appropriate for assessment of comparability in a rare disease population where traditional non-inferiority analyses are intractable/not feasible. Based on the actual observed 012 data, the minimum difference in GFR that the study was able to detect based on these criteria was 0.71 ml/min/1.73m^2/yr for eGFR and 1.24 ml/min/1.73m^2/yr for mGFR. Given the decline in GFR in untreated Fabry patients of -2 to -12 ml/min/1.73m^2/yr, these detectable differences are	However, in the interests of clarity the text has been amended as suggested: added to erratum (page 11).

sizes it was not possible to formally test noninferiority of migalastat compared to ERT for renal function." In relation to comparability criteria in ATTRACT, the ERG report states that 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 (pages 11, 55 and 57) and later refers to the criteria as 'ad hoc' (page 81).	renal outcomes in the migalastat and ERT groups had greater than 50% overlap." Please replace the text on page 57 with: As acknowledged in the CS, due to small sample sizes it was not possible to formally test non-inferiority of migalastat compared to ERT for renal function via the usual means so a different method was employed after agreement with the EMA. Page 81 Delete words "ad hoc "	acceptable and meaningful.	

Issue 3 Differences in baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12: "*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*	Please add: "However, none of these numerical differences were statistically significant".	It is important that the statistical significance of these differences is stated to provide the committee with a full understanding of the patients enrolled in the clinical trials. The ATTRACT study primary analysis was an ANCOVA that accounted for gender, baseline age, baseline GFR and baseline proteinuria. These are the parameters known to impact GFR	Not a factual inaccuracy. The ERG text accurately reflects the patient demographics at baseline. Lack of statistical significance is not meaningful here given the small sample sizes.

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)." Page 41: "*There are a number of imbalances in the patients' baseline characteristics between the migalastat and comparator arms in each trial*". Page 139: *"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."*		and they were statistically accounted for.	

Issue 4 FACETS eGFR reportedly inconsistent

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14: "*The FACETS trial also reported two different measures of eGFR, but these showed inconsistent changes from baseline.*"	On page 14 delete: "*The FACETS trial also reported two different measures of eGFR, but these showed inconsistent changes from baseline.*"	This is incorrect. There were not inconsistencies in the eGFR measures. Also CKD-EPi eGFR is the more accepted eGFR measure (versus MDRD eGFR) and should be used for interpretation. We request to have the eGFR CKD-EPi data included which show an annualized rate of change of [redacted] ml/min/yr which	Not a factual inaccuracy. ERG Tables 17 and 20 (sections 3.3.2.1 and 3.3.3.1) clearly report all three GFR outcomes and the text statement on page 14 accurately reflects the GFR data.

		is very stable.	

Issue 5 Data collected in FACETS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14: "*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.*"	Delete this statement.	This is incorrect. Quantitative data is available for all of these endpoints. The 24-month LVMi data shows a statistically significant reduction from baseline with migalastat treatment (reported in Table C9.22 of the CS). Data is available in the Galafold SPC or can be provided upon request.	Not a factual inaccuracy. CS Table C9.22 does not report changes in LVMi for both the trial arms.

Issue 6 Interpretation of HRQoL data in FACETS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15: "*Due to the short duration of the trial it is inadvisable to attempt to draw any firm conclusions about effects of migalastat on HRQoL.*"	Please delete this statement.	The ERG cannot suggest that the committee do not consider statistically significant and clinically meaningful results. The improvement in diarrhoea was statistically significant during the double blind placebo controlled period of FACETS. This improvement in diarrhoea was maintained over the 24 months of the open-label extension and additional statistically significant (95% CI of change from baseline did not overlap with zero) improvements were demonstrated in indigestion and constipation.	Not a factual inaccuracy. Short duration of follow up is a methodological limitation which the ERG has an obligation to point out. The GSRS results over 6 months are clearly reproduced in ERG Table 19 for the Committee to consider. The statistical significance interpretation is weak since no variance measures are given for the 6-month outcomes and only crude p-value thresholds are presented ($p<0.05$ or $p\leq0.05$).

			As stated in the ERG report, the CS appears selective in the way statistical parameters are reported (i.e. only p-value thresholds given for some outcomes, but confidence intervals for others).
Page 14: "*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*."	Change to: "*Changes in GSRS scores at 6 months showed a significant improvement in the diarrhoea domain between the 2 groups (−0.3 for migalastat vs. 0.2 for placebo, P<0.05). In a post hoc analysis of patients who had symptoms at baseline, there was also a significant difference in the scores for reflux at 6 months favouring migalastat (−0.5 for migalastat vs. 0.3 for placebo, P<0.05). There was no difference between the groups for indigestion, constipation or abdominal pain.*"	To have a significant result on criteria at 6 months but to say that this suggests an improvement and that it is inconclusive is a subjective interpretation. The trial was against placebo not ERT as reported by the ERG.	First part: not a factual inaccuracy. The ERG text on page 14 reflects the GSRS data in ERG Table 19. The ERG does not have confidence in the statistical significance of these outcomes since only crude p-value thresholds are reported which would not discriminate marginal from high statistical significance. Second part: "ERT" changed to "placebo": added to erratum (page 14).
Page 51: "*In addition, ATTRACT reported the SF-36 Mental Component Summary (0-100 scale), whilst FACETS employed the Gastrointestinal Symptoms Rating Scale (GSRS).*"	Please change to "*In addition, both ATTRACT and FACETS reported the SF-36 Mental Component Summary (0-100 scale), and FACETS also employed the Gastrointestinal Symptoms Rating Scale (GSRS).*"	FACETS also included the SF-36 Mental component and data are available on request.	Not a factual inaccuracy. The CS, manuscript by Germain et al., and the draft SPC and EPAR for migalastat do not mention the SF-36 Mental Component Summary in FACETS.

Issue 7 Dimensions of the Gastrointestinal Symptoms Rating Scale

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14: "*Quantitative HRQoL results were reported for the Gastrointestinal Symptoms Rating Scale (GSRS), but only for five of 15 possible symptom domains*."	Please amend to "*Quantitative HRQoL results were reported for the Gastrointestinal Symptoms Rating Scale (GSRS).*"	There are only 5 domains for the GSRS. There are 15 questions, but the questions are grouped into 5 domains: diarrhoea, constipation, abdominal pain, reflux, indigestion.	ERG inadvertently refers to an earlier version of GSRS. Text has been amended as suggested: added to erratum (page 14).

Issue 8 Severity of disease in patients in the clinical studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 34: "*the population of the ATTRACT trial excluded patients with ESRD and as such would not be reflective of patients with more severe Fabry disease.*" Page 41: "*the course of Fabry disease is generally different in men and women, and the clinical advisor to the ERG commented that progression is generally slower in women. However, the CS does not report baseline characteristics separately for males and females*" Page 41: "*The clinical advisor to the ERG also commented that,*	On page 34 delete the wording "*and as such would not be reflective of patients with more severe Fabry disease."* On page 41 change the following: "*However, the CS does not report baseline characteristics separately for males and females*" To "*The CS reports an analysis of baseline disease severity by gender which shows that in both studies, the majority of both*	This statement on page 34 is not accurate. Fabry disease is a multi-system disorder that affects multiple organs that manifests itself heterogeneously in different individuals; therefore the exclusion of patients with ESRD does not mean that patients do not have severe Fabry disease. For example, as shown in the ERG report Table 1, individuals with cardiac variant disease may have serious manifestations (non obstructive cardiomyopathy and myocardial infarction) prior to development of renal disease. The first statement on page 34 is incorrect as Table C9.9 of the CS presents a baseline assessment of disease severity by gender. Regarding the second statement on page 41, whilst we do not dispute the opinion of the clinical	ERG page 34: Not a factual inaccuracy. The proportion with ESRD in ATTRACT was lower than in the younger-aged Global Fabry Registry (as mentioned in ERG section 4.4.3). The proportions with cardiac and cerebrovascular events in ATTRACT were also lower than in the Registry. The ERG report clearly acknowledges on page 35 that limiting the trial population to those without ESRD is consistent with the SPC. ERG page 41: Text has been

based on the limited baseline information reported in the CS, the ATTRACT trial population does not appear to be severely affected by Fabry disease." Page 92: "*The ATTRACT trial enrolled patients with less severe manifestations than those expected in clinical practice. For instance, the ATTRACT study cohort included one patient with renal failure whilst in clinical practice it is likely that there would be a higher proportion of patients with this complication."* Page 138: "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."	*male and female patients had multi-organ involvement and suggests a reasonable disease burden for most patients*" On page 92 delete: "*The ATTRACT trial enrolled patients with less severe manifestations than those expected in clinical practice. For instance, the ATTRACT study cohort included one patient with renal failure whilst in clinical practice it is likely that there would be a higher proportion of patients with this complication."*	advisor, the report does not present a balanced view of the severity of disease in the patients included in the studies. In particular, there is no mention of Table C9.9 that presents a baseline assessment of disease severity and shows that In both studies, the majority of both male and female patients had multi-organ disease, the majority ([redacted]) had neuropathic pain and the majority ([redacted]) had had gastrointestinal symptoms. In addition all patients in ATTRACT were already eligible for and receiving ERT and were therefore already receiving the benefit of these treatments on their symptoms. The statement on page 91 is is not true since the patients treated in ATTRACT met guidelines for starting ERT and had received at least one year ERT treatment. In clinical practice patients with renal failure would not start treatment with migalastat since it is not recommended in these patients. All of the statements referenced here are misleading as they imply that the study populations had relatively mild disease and did not include patients with severe Fabry disease, which was not the case. Current guidelines suggest starting treatment in patients with a confirmed diagnosis and at least 1 major organ involvement. The patients enrolled in the migalastat clinical studies exhibited clinical manifestations that represent the full spectrum of disease severity. Overall, a majority of the amenable mutations that are characterised in the medical literature are associated with classic Fabry disease. In	amended to include the point made by the company about the baseline analysis by sex: added to erratum (page 41). ERG page 92: Not a factual inaccuaracy: clinical advice to the ERG was that the population in ATTRACT did not appear to be as severely affected by FD for their age as might be expected. However, we accept that the words "in clinical practice" could cause confusion since migalastat is contraindicated in people with ESRD. Text has been amended as suggested: added to erratum (page 92). ERG page 138: Not a factual inaccuracy. The statement is not referring specifically to the eligibility for migalastat therapy in clinical practice.

		FACETS, a majority of patients had mutations associated with the classic phenotype. Equal proportions of patients in ATTRACT had mutations associated with the classic and late-onset phenotypes. Analyses of baseline disease severity revealed that the male and female patients enrolled in FACETS and ATTRACT generally had substantial disease burden at baseline, with [redacted] of patients in Study AT1001-012 and [redacted] of patients in Study AT1001-011 having multi-organ disease involvement. The patients included in the Phase 3 migalastat studies reflect the general Fabry disease population, and are similar in extent and types of organ system involvement, and in level of renal impairment, to the patients included in the ERT patient registries and pivotal ERT trials. The study populations therefore reflect those that will be eligible to receive treatment in practice that is, any patient with an amenable mutation that is currently eligible for ERT, that does not have ESRD. Equally the NHS England SOP for Fabry disease 2013 have an exclusion criteria for ERT of end stage renal failure requiring dialysis in the absence of other starting criteria.	As noted above the patients had lower rates of ESRD, cardiac and cerebrovascular events than in the Global Fabry Registry and therefore may not be representative of the general Fabry disease population. However, patients in ATTRACT were older than those who would be started on ERT or migalastat and therefore may have had greater disease severity than patients initiating therapy.

Issue 9 Clarification of study phases and long-term follow-up

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 43: "*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. Stage 2 may refer to the first 6 months of the OLE following FACETS (i.e. months 6-12) or to the full OLE period (i.e. months 6-24), with stage 3, when mentioned, referring to the last part of the OLE (i.e. months 12-24) (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 ERG did not previously request clarification on this and their interpretation is inaccurate so we wish to clarify here. Figure C9.4 in the CS shows stages of the FACETS RCT: • Stage 1: Month 0-6 double-blind treatment period • Stage 2: Month 7-12 open-	On page 43, please change the following: *"Stage 2 may refer to the first 6 months of the OLE following FACETS (i.e. months 6-12) or to the full OLE period (i.e. months 6-24), with stage 3, when mentioned, referring to the last part of the OLE (i.e. months 12-24) (CS pages 115, 122 and CS Tables C9.5 and C9.28)."* To: *"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)."*	It is important to correct these statements since it is an incorrect representation of the study design and patients have been treated with migalastat for longer periods than is interpreted by the ERG. Patients from FACETS have been treated with migalastat for up to 9 years, and patients from both FACETS and ATTRACT can continue to receive migalastat for an indefinite period in study 041/042.	Text has been amended as suggested: added to erratum (page 43).

label treatment period • Stage 3 (not labelled as such in figure): Month 13-24 Open–label extension			
In Figure 5 (page 43) the ERG have interpreted that the open label-extensions of FACETS and ATTRACT equate to open-label treatment in study 041/042, which is not the case as they are separate and distinct phases: • In ATTRACT ERT experienced patients with an amenable mutation were either switched to oral migalastat 150 mg QOD or maintained their ERT for 18 months. The patients could participate in a 12-month open label extension. At the end of the study, the patients could participate in a long-term follow-up study (041/042). • In FACETS all patients received oral migalastat 150 mg QOD or matching placebo for 6 months (stage 1). Thereafter, patients on placebo were switched to migalastat 150 mg QOD for 6 months, and patients already on migalastat	Please delete or amend Figure 5 as it is incorrect.		Figure 5 has been amended to clarify patient flow through the different studies: added to erratum (page 44)

continued for another 6 months (stage 2). After the 12 months of the main study each patient could be enrolled in 12-months open label extension study (stage 3). At the end of the study patients could participate in a long-term follow-up study (041/042).			
Page 44: "*As shown in Figure 5, following completion of the 18-month randomised phase of ATTRACT and the 6-month randomised phase of FACETS, patients from both arms of each trial were eligible to receive 18 months of migalastat therapy in the OLE studies. Patients from ATTRACT could therefore receive a total of 18 months of migalastat therapy (ERT → migalastat) or 36 months of migalastat therapy (migalastat → migalastat).*" This is incorrect as patients in ATTRACT could receive 12 months treatment in the open-label extension (12 or 30 months total).	Please change the wording on page 44 to "*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*		Text describing Figure 5 has been amended as suggested to match the amended Figure: added to erratum (page 44)

	ATTRACT/FACETS open-label phases patients could continue to receive treatment with migalastat in the open-label extension studies 041/042"		
Page 52: "*In the context of adverse events reporting the ERG assumes that 'Stage 2' refers to the full 18-month OLE period*". This is incorrect as Stage 2 refers to month 7-12 (Figure C9.4).	Please change the text on page 52 to: "*In the context of adverse events reporting 'Stage 2' refers to the 7-12 month OLE period"*		Text has been amended as suggested: added to erratum (page 52)

Issue 10 Reliability of mGFR versus eGFR

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10: "*According to the literature and clinical advice received by the ERG, measured mGFR is more reliable than eGFR.*" Page 61: "*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."*	Please delete these statements.	Estimated GFR has several advantages over mGFR in a clinical trial setting. Given the invasiveness of mGFR, it is not feasible to determine mGFR frequently. Higher variability of mGFR results were expected and observed given that fewer measurements (four) were performed in the study, as compared to the eight assessments of eGFR. Furthermore, there are methodological challenges inherent in mGFR assessments; for example, mGFR is affected by protein intake, exercise, and diurnal variation (Stevens and Levey 2009), which contribute to variability. In contrast, eGFR based on serum creatinine concentration is commonly used to	ERG Page 10: Not a factual inaccuracy. Whilst the ERG notes that mGFR is considered to be more reliable than eGFR, the ERG report presents and discusses all three GFR outcomes.

		routinely monitor renal function in clinical practice (Weidemann et al., 2014), including in Fabry disease. Estimated GFR has been established as a reliable measure to monitor the progression of established chronic kidney disease (CKD) in clinical trial settings (Stevens and Levey, 2009). Estimated GFR is based on serum creatinine measurements performed in certified laboratories using a standardized procedure and can be performed frequently during the course of the study, thereby minimizing variability in the result.	

Issue 11 Interpretation of GFR analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14: "*For renal function (secondary outcome), the six-month change in mean (±SE) mGFR in the ITT analysis in FACETS was* [redacted] *mL/min/1.73m^2 in the migalastat group (n=34) and* [redacted] *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*	On page 14, please delete "*Although these results suggest that patients may have had better stabilisation of GFR in the placebo group than the migalastat group"*	Based on the data it is misleading to state that the results suggest that patients may have had better stabilisation of GFR in the placebo group than the migalastat group. As stated by the ERG conclusions about changes in renal function, especially given the relatively small sample sizes and large standard errors cannot be made.	Page 14: Not a factual inaccuracy. The ERG report directly refers to the numerical changes in GFR presented in the CS and clearly states that the short time duration, relatively small sample sizes, and relatively large standard errors make the interpretation of these changes uncertain.

and large standard errors."			
Page 14: "*However, this does not apply to the [redacted] analysis of $eGFR_{CKD-EPI}$ since the difference in this GFR outcome between the migalastat and ERT groups [redacted] the pre-specified 2.2 mL/min/1.73m^2"*	Please amend to: "*In the [redacted] analysis of $eGFR_{CKD-EPI}$ the difference between the migalastat and ERT groups [redacted] the pre-specified 2.2 mL/min/1.73m^2, however it is important to note that the result numerically favoured migalastat"*	This statement is misleading.	NB this comment refers to page 61, not page 14. Not a factual inaccuracy: the ERG text on page 61 accurately describes the GFR data.

Issue 12 Presentation of 30-month LVMI data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 74: "*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)*."	The data in patients with LVH at baseline should also be presented. Please add "*In patients with LVH at baseline, the reduction to month 30 for migalastat was statistically significant based on the 95% CIs (-10.0 [95% CI: -16.6, -3.3]).*"	The data presented ignores the fact that it may be difficult to show a statistical difference in the reduction of LVMi in a group that included patients without LVH at baseline.	Not a factual inaccuracy; however, it is a reasonable request from the company as the ERG report omits this relevant subgroup. Text has been amended as suggested and sample size added (erratum, page 74).

Issue 13 Statistics reported for cardiac outcomes in ATTRACT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 13 footnote: *"CS reports median with 95% CI – unclear whether this should be mean or report the IQR instead."*	Please change to mean.	This was incorrectly stated in the manufacturer submission.	Not an ERG factual inaccuracy; however, we have corrected this on behalf of the company: added to erratum (page 64).

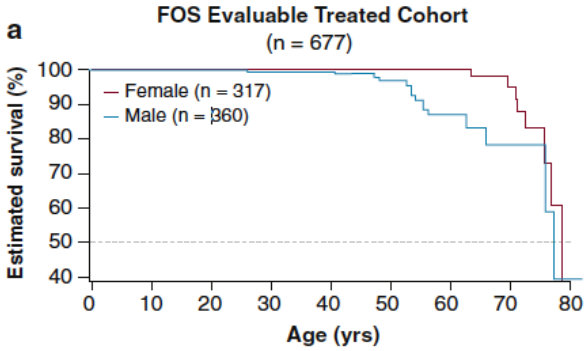
Issue 14 Data on activity of α-gal A in women

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 75: "*The activity of α-gal A in peripheral blood mononuclear cells* [redacted] *in males (CS pages 117-118); however, the CS does not report the findings for females or for the total amenable mutations population*" Page 77: "*except for α-gal A activity which was reported separately for males (but not separately for females), although this was not one of the pre-specified subgroup analysis*." Page 51: "*the activity of α-gal A enzyme itself was also measured in peripheral blood mononuclear cells as an outcome in both trials, but only reported for males in FACETS"*	Page 75 please change to "*The activity of α-gal A in peripheral blood mononuclear cells* [redacted] *in males (CS pages 117-118); Measurement of α-Gal A is only carried out in males due to the heterogeneous expression in different cells in females (through random inactivation of the X chromosome)."* Page 77 delete: "*except for α-gal A activity which was reported separately for males (but not separately for females), although this was not one of the pre-specified subgroup analysis*." Page 51 change to "*the activity of α-gal A enzyme itself was also measured in peripheral blood mononuclear cells as an outcome in both trials, and reported for males in FACETS*"	The wording implies selective reporting of data, which is not the case. The statements infer that data has not been reported for females where in fact this analysis was not carried out at all in female as explained on page 89 of the CS: "*Measurement of α-Gal A is only carried out in males due to the heterogeneous expression in different cells in females (through random inactivation of the X chromosome)*". *α-Gal A levels in females are inconclusive evidence of Fabry.*	Not factual inaccuracies. The company did not report that α-gal A activity in CS Table C9.13 was for males only - it was measured in both sexes according to the CS. However, the ERG does not wish to imply that this outcome was reported selectively, so text has been amended for clarification: added to erratum (pages 51, 75, 77).

Issue 15 Life expectancy predicted by the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Sourcing life expectancy of patients with Fabry disease from Waldek et al 2009 and estimating survival based on period life expectancies rather than cohort life expectancies. Page 23, 121 (Table 45), 121, 123, 126 (Table 48), 127, 128 (Table 50) *Analysis 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] Page 97: *"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*	The life expectancy of patients with Fabry disease should be sourced from Beck et al (2015), rather than Waldek et al (2009). The model estimated survival is therefore closer to current survival estimates for patients with Fabry disease (male survival 82.4 years in model, 77.5 years in literature). This difference in predicted life expectancy with the model and current survival estimates are due to the use of different methodologies from the Office for National Statistics for deriving survival estimates. Using period life expectancies for the model rather than cohort life expectancies results in an estimated age of death in males of 71.6 which would suggest than in fact the model slightly underestimates survival, rather than	Using Waldek et al to estimate life expectancy in ERT or migalastat treated patients is not appropriate because: • Those that died were much older at diagnosis than surviving patients (40.6 in males that dies vs. 26.5 in surviving males, 53.3 vs. 33.3 in females). This suggests that they may have been at a later stage of disease progression where ERT would have had less impact on slowing the disease. The publication states "The patients who died were diagnosed with Fabry disease at a relatively late age: median 40 years in males and 55 years in females. Accordingly, the disease had progressed substantially before these patients were diagnosed, which likely contributed to their early deaths." • They had also not been receiving ERT for long - 61 of the 75 deceased males (81.3%) and 5 of the 12 deceased females (41.7%) were known to have received ERT, which became commercially available in Europe 2001 and in the United States in 2003. The median length of time that these patients were on ERT was 12 months in males and 4 months in females. The publication states "These patients were untreated for the majority of their lives" and "the deceased patients were diagnosed	Not a factual inaccuracy. The ERG's view is that Waldek et al. provides a more robust estimate of the life expectancy of Fabry patients as it is based upon a much larger dataset and was more reflective of clinical opinion to the ERG than the study by Beck et al.

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." Page 111: *"The company's estimated life-expectancy is 83.4 years in Fabry patients who receive migalastat …. 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*	overestimates as suggested by the ERG. The ERG base case analysis should be based on cohort life expectancies (used by the manufacturer) rather than period life expectancies (used by the ERG), as cohort life expectancies are reflective of long-term outcomes that the model is predicting. Please remove any referral to "erroneous" life expectancy as it is not wrong, but rather is one of two available statistical methods to predict survival. If the ERG wishes to calibrate the model to current survival estimates rather than expected survival with migalastat or ERT, the model that uses cohort life expectancies should be calibrated to a male survival of 77.5 from Beck et al (2015) rather than the average life expectancy from Waldek et al (2009). The model based on period life expectancies should not be calibrated as it underestimates life expectancy compared to Beck et al (2015).	at a relatively late age and were therefore likely to have been in the advanced stages of Fabry disease at the time of diagnosis, as well as at the time they began receiving ERT." This demonstrates that basing survival on this publication is inappropriate as it is not representative of the treated cohort and is out of date. Note also that in this publication the expected life expectancy of males is stated to be 58.2 years and 75.4 for females (average 66.8, not 66.5 as stated in ERG report). Conversely, in a more recent and much larger study by Beck et al, estimated median survival in treated males was 77.5 years (n=360) (see figure below). Patients were diagnosed much earlier (males 27.9 year, females 39.1 years), which is consistent with current age at diagnosis. Patients had been treated for 5-years (median follow-up) which is shorter than would be expected on currently treated patients but more representative than the patient population evaluated by Waldek et al.	

disease patient on migalastat or ERT will outlive the average woman in the general population by about 5 months." Reference to erroneous survival estimates: page 18, 110, 112, 120, 122, 127.	If the ERG still wishes to present Analysis 4 as an additional sensitivity analysis rather than the ERG base case, the average survival should be corrected from 66.5 years to 66.8 years.	 Furthermore, expectations of life can be calculated in 2 ways: "period life expectancy" or "cohort life expectancy"[1]: • Period life expectancy at a given age is the average number of years a person would live, if he or she experienced the age-specific mortality rates for that time period throughout his or her life. It makes no allowance for any later actual or projected changes in mortality. In practice, death rates of the area are likely to change in the future, so period life expectancy does not therefore give the number of years someone could actually expect to live. • Cohort life expectancies are calculated using age-specific mortality rates that allow for known or projected changes in mortality in later years and are thus regarded as a more appropriate measure of how long a person of a given age would be	

[1] http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/guide-method/method-quality/specific/population-and-migration/demography/guide-to-period-and-cohort-life-expectancy/index.html

		expected to live, on average, than period life expectancy. Cohort life expectancies have been used in the model as these are more representative of the long-term costs and outcomes expected for the Fabry disease cohort. Since healthcare is continually improving, the majority of economic models use cohort life expectancies for modelling mortality. However, for validation against current survival estimates for patients with Fabry disease, the use of period life expectancies is required, as has been conducted by the ERG.	

Issue 16 Time-dependency of transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 89*: "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."* *"The greatest deficiency of the model is the structural and parameter assumption of constant transition probabilities that are too low to be realistic"*	Please provide an accurate reference that demonstrates that transition probabilities should vary with time. If a definitive reference is not available, please amend the wording to reflect that it is the ERG's belief that the transition probabilities may increase with time, which would lead to a reduced life expectancy than currently modelled.	Reference 46 is to Eng et al (2007) but the publication does not appear to show any evidence that the risk of progression increases over time. It is not implausible that transitions are constant over time. The transition probabilities used in the model are based on data from Rombach et al which shows a fairly linear Kaplan Meier curve for time to first symptoms (see Figure 2 of publication). The disease of course progresses over time, which leads to an increased number of symptoms over time, which is reflected by the model structure and the transition probabilities. Fabry disease is a heterogeneous disease and as such a patient may progress to complications anywhere between 5 and 80 years of age (Eng et	Not a factual inaccuracy. Age related incidence in chronic diseases such as coronary heart disease and renal disease are well known and it is standard practice to use age related probabilities to model these. Fabry disease patients are at risk of progressing to CHD and ESRD. Weidemann et al. 2013 (Journal of Internal Medicine) shows a Figure demonstrating that the incidence of major events increases with age.

		al, 2007). The transition probabilities used in the model are based on published data from the Dutch registry – they are model based on observed transitions between complications states. Page 123 of the ERG report states that the ERG "could not identify better time-dependent transition probabilities" which implies that the company has utilised the best available evidence. Given that NICE conducts evidence-based decision-making, it would seem apparent that utilising transition probabilities from a peer-reviewed publication is more robust than applying an arbitrary multiplier to transitions matrices.	

Issue 17 EQ-5D tariff used in the cost-consequence model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG has incorrectly interpreted that the Dutch tariff was used to value the EQ-5D utilities. Page 86, 87 and Table 25 *"In general, the company model is in line with the NICE reference case… The tariff used for the EQ-5D was not from the UK population."*	Change Table 25: • "Source of preference data: Representative sample of the UK population" should be "Yes" • "The tariff used was from a Dutch population" to "The tariff used was from a UK population." Delete *"Fourthly, the tariff used for the EQ-5D was not from the*	Rombach et al cites Dolan et al (1997) for the valuation of the EQ-5D, which is the UK tariff. The publication also states in the sensitivity analysis section: *"Mean health utilities by disease state based on preferences from the Dutch general populations are non-significantly higher than the UK based data [17], with lower losses in health utility during disease progression. Hence, slowing disease progression results in less QALYs to be gained, if Dutch preferences were to be used instead. Consequently, the ICERs lie above the UK based*	We agree. The text has been amended in Table 25 (page 86) and on page 87: added to erratum (pages 86, 87).

	UK population."	*values reported in this paper."* We have also received written confirmation from the corresponding author (Marcel Dijkgraaf) that the authors used the UK tariffs in the main analyses and addressed the Dutch perspective in sensitivity analyses.	

Issue 18 Evidence synthesis for model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 86, 87 and Table 25 *"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…. 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."*	Please remove this statement as the evidence is in line with the NICE reference case. The relevant row of Table 25 should state: Yes – a systematic review identified that the most relevant evidence on effectiveness came from the comparative trial evidence, from which the manufacturer assumed clinical equivalence.	The NICE reference case for the Synthesis of evidence on health effects (section 5.2 of the Guide to the Methods of Technology Appraisal, 2013) states that "The Institute has a preference for RCTs directly comparing the intervention with 1 or more relevant comparators and these should be presented in the reference-case analysis if available." and "RCTs directly comparing the technology under appraisal with relevant comparators provide the most valid evidence of relative efficacy." We have conducted a systematic review of all clinical evidence and the most relevant study for the appraisal of migalastat is the ATTRACT trial since it is a randomized comparative clinical trial. A statistical evidence synthesis/ mixed treatment comparison is not possible (as acknowledged in the ERG report).	ERG pages 86, 87 and Table 25: not a factual inaccuracy. The model has not used any of the clinical outputs from the systematic review in the modelling.

Issue 19 Validity of disutility values obtained from DCE for infusion burden

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 18: *"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."* Page 103: *"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*	Delete "*This is clearly unrealistic*" on page 18 Keep first sentence "*The utility values from this study*……" The remaining sentences should be reworded to reflect that although the NICE reference case is the EQ-5D, it may not be appropriate for all cases (NICE Guide to the methods of technology appraisal, 2013; 5.3.10) and is unlikely to be appropriate for measuring the disutilities of administration methods given the 5 domains and recall period.	It is important that decision-making is based on the best available evidence. Utilities associated with infusions for ERTs have not previously been elicited so Amicus commissioned a de novo study based on a DCE framework. It is important to strike the balance between pragmatism and methodological rigidity. The DCE was a large (>500) representative sample of the UK general public rather than people with Fabry disease. NICE state that they wish to see health outcomes data used in models which have been weighted by preferences from the general public and this is a strength of the research. Generic instruments designed to derive utilities from patient samples, such as the EQ-5D or Health Utilities Index may not have items or response options that are sensitive to specific treatment attributes[2]. The EQ-5D would not capture the difference of an infusion as it asks about your <u>health today</u>. The only way to be able to capture the infusion burden would be to ask a person to complete the EQ-5D at the very moment that they are receiving an infusion, in which case they would be	Not a factual inaccuracy. The ERG has stated our opinion on estimates given for disutility for an ERT infusion.

[2] Garau M, Shah KK, Mason AR, Wang Q, Towse A, Drummond MF. Using QALYs in cancer: a review of the methodological limitations. Pharmacoeconomics. 2011;29(8):673–685)

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."		immobile, unable to do their usual activities (because they are attached to an IV) and possibly in some discomfort/pain due to the IV so would probably record a very low EQ-5D. The reported values from the DCE and Matza et al (2013) are similar. The Matza values are lower but this is not surprising as these are from cancer patients who are not receiving lifelong treatment unlike those with Fabry disease who would be receiving intravenous infusions every other week for the rest of their life. The ERG view that the disutility estimate for EQ-5D would be lower than seen in the DCE is not substantiated by specific examples of appraisals that are referred to. It also ignores the very real burden of having intravenous infusions every other week for life (as described in the company's submission – *UK Fabry Infusion Survey)*. Adverse effects, whilst incurring a disutility, may be relatively short lived or manageable so the ERG statement is conjecture. The published data and our study concur. It is academically inappropriate of the ERG to arbitrarily pick a disutility that they feel is appropriate when there is a large, well-conducted study available. Amicus is of the view that the DCE approach is the more pragmatic, methodological and relevant approach for utility elicitation in this instance.	

Issue 20 Utility values from Rombach et al (2013) based on low numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 102, third paragraph *"These utility values have been based upon a small number of patients."*	Please delete this statement.	The Rombach et al (2013) paper has utilities from 75 patients. The ERG make reference to the Miners et al (2002) publication and use the utility values for cardiac complications and stroke in their scenario 7 analysis. The ERG has neglected to acknowledge that these values are also, not surprisingly considering the rarity of Fabry disease, based on small numbers of patients and are not that dissimilar to Rombach et al. The Miners et al (2002) paper collected EQ-5D data on 38 patients. Therefore to criticise that the utilities used from Rombach et al in the company submission are based on small numbers and not acknowledge those from Miners et al are also based on small numbers is misleading.	Not a factual inaccuracy. The ERG acknowledges that there are also small numbers in the study by Miners et al.

Issue 21 Number of patients with EQ-5D results in Miners et al (2002) is incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 102, fourth paragraph "*Miners and colleagues[53] collected EQ-5D utility values for 53 patients in UK with Fabry disease. The values are reported*	Change to "*Miners and colleagues[53] collected EQ-5D utility values for 38 patients in UK with Fabry disease. The values are reported as a*	The Miners et al (2002) paper collected EQ-5D data on 38 patients not 53.	We agree. The value in the text has been changed from 53 to 38: added to erratum (page 102).

as a disutility for stroke (−0.28), cardiac symptoms (−0.20).”	*disutility for stroke (−0.28) n=5, heart symptoms (−0.20) n=28.”*		

Issue 22 Comparing baseline health state distribution to published data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 111: *“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 colleagues46 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 colleagues46 and starting patients at an earlier age to correct these discrepancies*	Please adjust this paragraph to accurately reflect that the modelled events are not at a mean age of 48 and also that the Eng data is not baseline data, but rather the total proportion of patients that experienced the event over a lifetime.	This is incorrect. The model starts at age 48 but that does not mean that everyone had the event at age 48. It is based on medical history data so events have happened in the past (we do not have the data on the specific age of event). Therefore the mean age of event for the model data will likely be less than 48. Furthermore, the Eng data is the proportion of patients that experienced the clinical event. Comparing this to the model baseline data is not appropriate because the model patients may go on to develop the event through model progression so you are not comparing like-for-like. This suggests that the total percentage with cardiac complications in the model will be more than Eng but the definition of cardiac complications is slightly different between Eng and the model. We therefore do not think that this is a credible scenario to present but note it has little impact on the results.	Not a factual inaccuracy. As stated in Eng et al. page 188: The mean (SD) current ages of the Fabry males and females were 36.5 (15) and 40.8 (17) years, respectively.

(section (4.4.*"*			

Issue 23 Certain company submission scenario analyses are not justified

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 117: *"Two of the analyses have assumptions which are insufficiently justified: the assumptions for the analysis wherein patients began treatment at age 16; and the assumption of improved efficacy (which is based on insufficient evidence). The ERG believes that these analyses should be considered illustrative only. Furthermore, several analyses expose limitations of the utility and disutility estimates."*	This paragraph stating that two of the analyses have assumptions that are insufficiently justified should be removed.	All scenario analyses are essentially illustrative similar to the ones that the ERG use where in their Scenario 8 and 9 the disutility for infusions is reduced by 50% and 75% respectively without any credible justification. Migalastat is indicated for adults and adolescents aged 16 years and older. Therefore an analysis where patients begin treatment at the age of 16 years is entirely appropriate. In addition, recent NICE appraisals have expressed a preference for the model baseline to be the age that a patient could start treatment, rather than the mean age of patients in a clinical trial (NICE appraisal of ataluren for Duchenne muscular dystrophy). In addition on page 122 of the ERG it is stated that: "*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."* This indicates that the ERG accepts patients may start treatment at the age of 16 and so to say the company submission analysis for this age is insufficiently justified is contradictory. It is reasonable to model a scenario where efficacy is improved by migalastat compared to ERT as has been demonstrated in the ATTRACT	We agree. Reference to the analysis that begins at age 16 years has been removed: added to erratum (page 117).

		study and its extension phase - this was justified in the company submission.	

Issue 24 Rounding of vials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 104: *"The company assumes that the number of vials per person is rounded down to the nearest vial."*	*"The company assumes that the number of vials per person is rounded up to the nearest vial."*	In the company submission the number of vials are rounded up, not down.	We agree. The sentence has been changed to say the number of vials is rounded up, as suggested: added to erratum (page 104).

Issue 25 Credibility and validity of company's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 89: *"The model fails to produce credible results"* Page 112: "*The model fails external validity checks and lacks face validity.*" Page 127: *"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."*	Delete the first two sentences. Amend the sentence on page 127 to: "The ERG believe some of the assumptions in the company's model are implausible and that many of the key model parameters lack validity, therefore we consider the ERG base case more plausible than the company base case."	A key component of the ERG validation was to compare the model predictions to historical life expectancies with Fabry disease. Whilst the model may contain limitations as for every economic model and the ERG may disagree with the modelling approach and framework taken, it is insufficient to declare that the model does not have face validity based on this. The ERG has not appreciated that the challenges in economic modelling based on rare disease evidence and Amicus believes it has taken an approach that enables decision-making. Further the results that the ERG has generated regarding costs and QALYs after their own modifications are not that different to the values	ERG pages 89, 112, 117: Not a factual inaccuracy. The ERG is stating our opinion on the validity of the model and the model results.

		presented in the company submission. As outlined in Issue 15, the company model used mortality statistics that predict future life expectancy and therefore cannot be validated against historical data. To compare against historical data, we have now conducted a scenario using period life expectancies (as per the ERG analysis) which results in the modelled Fabry disease patient cohort having a life expectancy less than reported survival with Fabry disease by Beck et al (2015). This is therefore consistent with the burden of Fabry disease described in the literature.	

Issue 26 Modelled patient weight

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 90: "*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 a trial of agalsidase beta by Banikazemi and colleagues, 88% of the trial population were male with a mean age of 46.9 years, and a mean weight of 70.1 kg … A trial of agalsidase alfa by Schiffman and colleagues had 26 males with a mean weight of 74.83 kg and a mean age of 34.18 years*	Please add: When assessing other RCTs of ERT in Fabry disease, three other historical multinational studies reporting patient weights from over 10 years ago were identified. These trials may not accurately represent the current weight of patients with Fabry disease in the UK.	The trials reported by the ERG with low starting weights were published at least 10-15 years ago, during which time the average weight of the UK population has increased. An inability to gain weight is a symptom of Fabry disease that can be corrected by ERT (Schiffman et al, 2001). The referenced studies were generally in treatment naïve patients so are likely to have included patients unable to gain weight and therefore reducing the mean weight of the cohort. Patients enrolled into ATTRACT were previously treated with ERT so any weight symptoms are likely to be better controlled. Therefore, the average weight in ATTRACT is more reflective of the current mean weight of	Not a factual inaccuracy. The ERG considers that using the patient weight from the ATTRACT trial is more plausible than using patient weight from the general population.

… It appears likely that the company base case analysis overestimates the body weight of patients receiving ERT."		patients with Fabry disease as ERT is the standard of care. During interviews with several KOLs across the UK, experts referred to the weight of the UK patients as being the same as the general population. A recent publication from Sweden showed the average weight of the Fabry cohort to be 76.5 kg (Johansson et al, 2015).	

Issue 27 Patients with ESRD treated with migalastat

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 112: *"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* .(4.4*"* "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." Page 139: "The model assumes that patients who develop ESRD continue to have migalastat treatment although the	Please amend page 112 to: The ERG notes that the migalastat SmPC states that migalastat is not recommended in patients with ESRD. The company has clarified that clinical expert opinion is that patients will not be started on migalastat if they have ESRD but it is unlikely that a patient would be taken off treatment if they developed ESRD whilst receiving migalastat. In the company base case, the model allows patients with ESRD to continue treatment with migalastat. The ERG has explored a sensitivity analysis in which patients come off treatment upon transition to the	The SPC for migalastat states that: • Galafold has not been studied in patients with Fabry disease who have a GFR less than 30 mL/min/1.73m^2 • Galafold is not recommended for use in patients with Fabry disease who have estimated GFR less than 30 mL/min/1.73m^2 Therefore no patients with ESRD would be started on treatment with migalastat. However, clinical experts have cited that it is highly unlikely that a clinician would remove a treatment that is having a positive impact on renal outcomes as it may accelerate the patients decline. Therefore, if a patient develops ESRD whilst receiving treatment with migalastat, it is unlikely that treatment would be stopped. Consequently, ESRD is a "starting rule" for migalastat as opposed to a "stopping	ERG pages 112, 139: not a factual inaccuracy. The ERG received advice from our clinical expert that patients would be likely to discontinue migalastat if they progress to ESRD because migalastat is contra-indicated in patients with ESRD.

marketing authorisation does not allow this."	ESRD state (section .(4.4 Please delete the statement on page 139.	rule". As stated in the CS, clinical experts have stated that they would follow existing Fabry disease guidelines when treating with migalastat. Therefore, an occasion in which treatment with migalastat and ERT would be stopped is if the patient developed ESRD and heart failure. This has not been explicitly modelled because heart failure is not a specific state (it is captured within cardiac complications).	

Issue 28 Incorrect results in Analysis 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 48: Total ERT costs 2,627,464 Total incremental costs [redacted]	Please amend to: Total ERT costs 2,700,840 Total incremental costs [redacted]	This appears to be a transcriptional error in the report.	We agree. The numbers have been corrected: added to erratum (page 126).

Issue 29 Antibodies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 24: *"Antibody reactions to ERT are usually easily controlled with infusion rate reductions and administration of pre treatment medications"*	Please add: Neutralising antibodies can occur to ERT, which have been shown to reduce the effectiveness of ERT (Lenders 2015).	This omission does not take into account neutralising antibodies which have been shown to reduce the effect of ERT, and predict worse outcomes so it erroneous to suggest that antibodies are controlled easily.	Not a factual inaccuracyr, since antibody reactions can often be easily controlled. However, we agree that the point about antibodies reducing ERT effectiveness is not made, so may appear unbalanced. Text has

			been amended: added to erratum (page 24).

Issue 30 Migalastat Assay

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39: *"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."*	Delete this statement.	Both trials had recruited based on the original HEK assay. Once the assay went through GLP there were some minor amendments and reclassification of mutations that were either amenable or non amenable. The relative numbers and proportions of participants who had such mutations that were reclassified was outside of the control of the study coordinators, so the effect on each trial was down to the change allocation in each arm. This has already been explained in the CS document.	Not a factual error. The ERG is merely noting that there are imbalances in the proportions of patients found not to have amenable mutations.

Additional points of clarification

Clarifications that were not previously requested by the ERG but that are queried in the report are provided here.

Description of problem	Clarification	ERG Response
Page 36: "*Justification for the sample size is not provided for either trial."* Page 53: "*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]"	**Sample size calculation in ATTRACT** (ATTRACT Study Protocol): The planned enrollment was [redacted] **Sample size calculation in FACETS** (FACETS Study Protocol): • To provide adequate power to test the primary outcome, [redacted]	Information noted – but not a factual inaccuracy (information was not provided by the company during the timescale for the ERG's appraisal of the CS)
Page 73: *"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"*	The 30-month efficacy data only include patients originally randomised to receive migalastat. 49 patients included in the safety analysis were from both the ERT and migalastat.	Information noted – but not a factual inaccuracy (information was not provided by the company during the timescale for the ERG's appraisal of the

		CS)
Page 99: *"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."*	One of the cases of dyspnoea in the ERT arm was classified as a serious adverse event.	Information noted – but not a factual inaccuracy (information was not provided by the company during the timescale for the ERG's appraisal of the CS)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Patient access scheme evidence submission template

July 2015

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for highly specialised technologies. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a highly specialised technology evaluation, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical effectiveness and value for money of a technology, in the context of a highly specialised technology evaluation, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Highly Specialised Technologies Interim Evidence Submission Template' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/hst-interim-evidence-submission-template.doc) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the highly specialised technology evaluation process, please see NICE's 'Interim methods and process statement for highly specialised technologies' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf). The 'Highly Specialised Technologies Interim Evidence Submission Template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the highly specialised technology evaluation, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated.

If you are submitting the patient access scheme at the end of the evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the highly specialised technology and the disease area to which the patient access scheme applies.

Galafold (migalastat) for the treatment of patients with Fabry disease, aged 16 years or older and with an amenable mutation to migalastat.

3.2 Please outline the rationale for developing the patient access scheme.

This patient access scheme is for provision of migalastat at a discounted price. This scheme is being provided to improve the value for money of migalastat with the expectation that it will allow a positive recommendation from NICE.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

It is a simple scheme with a fixed price (which will not vary with any change to the UK list price).

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The scheme applies to the whole licensed population.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain

criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme will always apply to all patients; there are no scheme criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable; there are no scheme criteria.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The scheme fixed price will be applied to all original invoices for migalastat.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The scheme is a simple discount so there are no administration requirements. For reference, NHS organisations will be provided with a notification document regarding the Terms and Conditions at the start of the scheme.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable; the scheme fixed price will be applied to all original invoices for migalastat.

3.10 Please provide details of the duration of the scheme.

As this is a simple scheme it would be in place from the date of guidance publication until NICE next reviews the guidance on migalastat and a final decision has been published on the NICE website.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No equity or equality issues have been identified.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

NHS organisations will not be required to complete an agreement form prior to participation in the scheme. A notification document regarding the Terms and Conditions will be provided for reference only.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

4 Value for money

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence'. You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Not applicable; the scheme population is the same as presented in the manufacturer submission of evidence for the NICE evaluation.

4.2 If you are submitting the patient access scheme at the end of the highly specialised technology evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

Not applicable; the patient access scheme is being submitted prior to the NICE committee meeting.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the HST Evaluation Committee considered most plausible.

The pack price of migalastat (14 tablets) has been reduced from the list price of £16,153.85 to the patient access scheme price of [redacted]. This has reduced the cost of migalastat per annum from £210,000 to [redacted].

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable; the clinical effectiveness data is the same.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. .

Not applicable; there are no costs associated with the implementation or operation of the scheme.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable; no additional treatment-related costs would be incurred by implementation of the scheme.

Summary results

Base-case analysis

4.7 Please present in separate tables the economic results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 1 Base-case value for money results without patient access scheme

	Intervention (migalastat)	Comparator (ERT)
Intervention cost (£)	3,989,923	2,581,037
Other costs (£)	34,127	174,340
Total costs (£)	4,024,050	2,755,377
Difference in total costs (£)	N/A	1,268,674
LYG (or other outcome)	19.00	19.00
LYG difference	N/A	0.00
QALYs (or other outcome)	14.33	13.36
QALY difference	N/A	0.98

LYG: life-year gained; QALY: quality-adjusted life-year

Table 2 Base-case value for money results with patient access scheme

	Intervention (migalastat)	Comparator (ERT)
Intervention cost (£)	[redacted]	2,581,037
Other costs (£)	34,127	174,340
Total costs (£)	[redacted]	2,755,377
Difference in total costs (£)	N/A	[redacted]
LYG (or other outcome)	19.00	19.00
LYG difference	N/A	0.00
QALYs (or other outcome)	14.33	13.36
QALY difference	N/A	0.98

LYG: life-year gained; QALY: quality-adjusted life-year

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

See Table 1 and Table 2.

[2] For outcome-based schemes, please see section 5.2.9

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation. Consider using tornado diagrams.

Results of the deterministic one-way sensitivity analysis are presented in Figure 1 and Table 3 (comparable to Figure D12.7 and Table D12.32 of the main submission). Results for variations in parameters that do not affect cost results have been excluded (e.g. utilities and duration of adverse events).

Figure 1 One-way sensitivity analysis results with patient access scheme

Table 3 One-way sensitivity analysis results with patient access scheme

Parameter	Down	Up
% females in Fabry	[redacted]	[redacted]
Disease progression for untreated patients	[redacted]	[redacted]
Disease progression for treated patients	[redacted]	[redacted]
Discontinuation: ERT patients	[redacted]	[redacted]
Discontinuation: Migalastat	[redacted]	[redacted]
Annual risk of AEs: ERT	[redacted]	[redacted]
Annual risk of AEs: Migalastat	[redacted]	[redacted]
Discount rate costs	[redacted]	[redacted]
Acute event cost: CEFD	[redacted]	[redacted]
Acute event cost: cardiac complications	[redacted]	[redacted]
Acute event cost: ESRD	[redacted]	[redacted]
Acute event cost: Stroke	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]
Cost of health care provider contacts	[redacted]	[redacted]
Annual follow-up cost: all Fabry patients	[redacted]	[redacted]
Annual follow-up cost: cardiac complications	[redacted]	[redacted]
Annual follow-up cost: ESRD	[redacted]	[redacted]
Annual follow-up cost: Stroke	[redacted]	[redacted]
Market share of agalsidase alfa or agalsidase beta	[redacted]	[redacted]

4.10 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation.

Results of the scenario analysis are presented in Table 4 (comparable to Tables D12.33 and D12.34 of the main submission). Results for scenarios with different utilities that do not affect cost results have been excluded.

Table 4 Scenario analysis results with patient access scheme

Scenario	Incremental costs
Base case	[redacted]
ERT discount 0%	[redacted]
ERT discount 5%	[redacted]
ERT discount 7%	[redacted]
Reduced efficacy of ERT due to antibodies	[redacted]
Mean age of starting cohort 16 years	[redacted]
Average patient weight from ATTRACT	[redacted]
Societal perspective	[redacted]
Improved efficacy of migalastat over ERT to reflect results on composite endpoint observed in ATTRACT	[redacted]
Time horizon 20 years	[redacted]
Equal market share of ERTs	[redacted]

4.11 If any of the criteria on which the patient access scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme

4.12 For financially based schemes, please present the results of the value for money analyses showing the impact of the patient access scheme on the base-case and any scenario analyses. If you are submitting the patient access scheme at the end of the evaluation process, you must include the scenario with the assumptions that the HST Evaluation Committee considered to be most plausible.

Results of the base case budget impact analysis are presented in Table 5 (comparable to Table D13.6 of the main submission).

Table 5 Budget impact results with patient access scheme

	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]

Results of sensitivity analysis on budget impact are presented in Tables 6 and 7 (comparable to Tables D13.7 and D13.8 of the main submission). [redacted]

Table 6 Sensitivity analysis on ERT discount rate

ERT discount	Year 1	Year 2	Year 3	Year 4	Year 5
0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case: 3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7 Sensitivity analysis on budget impact

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean 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]

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

A Simple PAS notification to Trusts document has been attached.

CONFIDENTIAL UNTIL PUBLISHED

Migalastat for the Fabry disease

ERG overview of company Patient Access Scheme (PAS)

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Introduction

Amicus has provided a patient access scheme (PAS) for migalastat for patients with Fabry disease. This is a simple discount on the UK list price. The current UK list price is £16,153.85 per 14 tablet pack. The company has proposed a discount of [redacted] so that the cost per pack available to NHS England will be [redacted].

The company has provided a submission with details of the PAS and the updated results of their economic model. The ERG received this on 7th September 2016 and was requested by NICE to check the company's implementation of the PAS in the company's model, and re-run the ERG exploratory analyses to incorporate the discount.

The company's updated analyses

The ERG has checked the implementation of the discount in the economic results from the cost-consequence model and the budget impact model, identifying no errors in the findings. The results of the company analyses with PAS assumes a 3% discount for ERT. The results of the company's PAS base-case analysis with this 3% assumed discount for ERT are reported in Table 1.

Table 1 Base-case cost-consequence analysis results with PAS discount

Intervention	Costs	Incremental Costs	QALY	Incremental QALY
Migalastat	[redacted]		14.33	
ERT	2,755,377	[redacted]	13.36	0.98

In addition to the base-case cost-consequence analysis, the company presented the results of their one-way sensitivity analyses as tornado diagrams and tables for costs. The ERG identified no errors in the tornado diagram or the table. Figure 1 shows the tornado diagram for costs with PAS.

Figure 1 One-way sensitivity analysis results with patient access scheme

Table 2 reports the five-year budget impact after the introduction of migalastat. The ERG found no errors in the reported values.

Table 2 Estimated budget impact for the NHS and PSS (with the PAS discount)

	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]
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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]

ERG analyses using the migalastat PAS discount

The results of the ERG's exploratory scenario analyses in the cost-consequence model updated with the PAS discount are shown in Table 3 and Table 4. The ERG analyses do not assume a 3% discount for ERT, but instead use the list price. A separate confidential addendum has been prepared using CMU confidential pricing for ERT. Table 3 presents ERG scenario analyses 0 through 9; Scenario 0 represents the company base-case analysis using the list price for ERT. Table 4 presents the fully incremental analysis of the ERG base case (which is Scenario 10 in the ERG report and combines Scenarios 1-8).

Table 3 Results of the ERG's scenario analyses in the cost-consequence analysis with PAS discount

		Costs (£)			QALY		
#	Description	Migalastat	ERT	Incremental	Migalastat	ERT	Incremental
0	Base Case (no ERT discount)	[redacted]	2,835,202	[redacted]	14.33	13.36	0.98
1	ERG population (age 40, complications from Eng 2007)	[redacted]	3,034,104	[redacted]	15.35	14.30	1.04
2	ONS England & Wales Mortality (2012-14)	[redacted]	2,713,788	[redacted]	13.66	12.73	0.93
3	ATTRACT patient weight	[redacted]	2,700,840	[redacted]	14.33	13.36	0.98
4	66.5 year undiscounted life-span (Waldek et al 2009)	[redacted]	1,874,896	[redacted]	9.03	8.40	0.63
5	Equivalent discontinuation	[redacted]	2,835,202	[redacted]	14.33	13.36	0.97
6	No migalastat with ESRD	[redacted]	2,835,202	[redacted]	14.31	13.36	0.96
7	ERG health state utilities	[redacted]	2,835,202	[redacted]	13.87	12.89	0.98
8	50% infusion disutility	[redacted]	2,835,202	[redacted]	14.33	13.84	0.49
9	25% infusion disutility	[redacted]	2,835,202	[redacted]	14.33	14.09	0.25

Table 4 ERG Scenario 10, ERG base-case analysis

Comparator	Costs (£)	Incremental Costs (£)[1]	QALYs	Incremental QALYs[1]

Migalastat	[redacted]		11.00	
ERT (blended)	2,196,454	[redacted]	10.66	0.34
Agalsidase beta	2,047,431	[redacted]	10.66	0.34
Agalsidase alfa	2,260,321	[redacted]	10.66	0.34

[1]Incremental comparisons are to migalastat