CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

MIGALASTAT (GALAFOLD)

(Amicus Therapeutics)

Indication: Fabry Disease

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Abbreviations

alpha-Gal A	alpha-galactosidase A
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
BPI	Brief Pain Inventory
CFA	Canadian Fabry Association
CFDI	Canadian Fabry Disease Initiative
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVC	central venous catheter
CORD	Canadian Organization for Rare Disorders
eGFR	estimated glomerular filtration rate
$eGFR_{CKD-EPI}$	estimated glomerular filtration rate as measured by the Chronic Kidney Disease Epidemiology Collaboration equation
$eGFR_{MDRD}$	estimated glomerular filtration rate as measured by the Modification of Diet in Renal Disease equation
EQ-5D	EuroQoL 5-Dimensions questionnaire
ERT	enzyme replacement therapy
FD	Fabry disease
Gb3	globotriaosylceramide
GFR	glomerular filtration rate
GI	gastrointestinal
GL-3	globotriaosylceramide
GLA	gene for alpha-galactosidase A
GSRS	Gastrointestinal Symptoms Rating Scale
HCl	hydrochloride
HEK	human embryonic kidney
HRQoL	health-related quality of life
IBS	irritable bowel syndrome
ITT	intention-to-treat
LVEF	Left ventricular ejection fraction
LVMI	left ventricular mass index
LVPWT	left ventricular posterior wall thickness
Lyso-Gb3	globotriaosylsphingosine
MCID	minimally clinically important difference
MCS	mental component summary
MID	minimally important difference

MDRD	Modification of Diet in Renal Disease
$mGFR_{iohexol}$	measured glomerular filtration rate as assessed by plasma clearance of iohexol
mITT	modified intention-to-treat
OLE	open-label extension
PCS	physical component summaries
PP	per-protocol
PUD	peptic ulcer disease
RCT	randomized controlled trial
RI	renin inhibitor
SAE	serious adverse event
SD	standard deviation
SEM	standard error of mean
SF-36	Short-Form 36-Item Health Survey
TEAE	treatment-emergent adverse event

Drug	Migalastat (Galafold)
Indication	Long-term treatment of adults with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase [alpha-Gal A]) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay.
Reimbursement request	As per indication
Dosage form(s)	123 mg oral capsules
NOC date	September 5, 2017
Manufacturer	Amicus Therapeutics, Inc.

Executive Summary

Introduction

Fabry disease (FD), also called Anderson-Fabry disease, is an X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal alpha-galactosidase A (alpha-Gal A) activity, resulting in the accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in lysosomes in cells throughout the body.[1-3] Beginning early in life, this accumulation progressively affects organ function, leading to the serious and life-limiting sequelae of the disease, including neuropathic pain, skin disorders, progressive and severe renal impairment, pulmonary manifestations, cardiac problems including arrhythmia and cardiomyopathy, central nervous system involvement including cerebrovascular events, and early mortality.[1] Consequently, FD has a devastating effect on both quality and length of life, as patients deal with a variety of systemic symptoms and progressive organ damage. The manufacturer indicated that as of March 2017, data obtained from the Canadian Fabry Disease Initiative (CFDI) suggests that there are currently 424 FD patients in Canada, of whom 90 (21.2%) have been identified as having mutations amenable to treatment with migalastat. Of these, 44 currently receive enzyme replacement therapy (ERT) and are over the age of 16 years.[4]

Migalastat has a Health Canada indication for long-term treatment of adults with a confirmed diagnosis of FD (deficiency of alpha-Gal A) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay.[5] The Health Canada–recommended dose in adults 18 years and older is 123 mg migalastat (one capsule) once every other day at the same time of day.[5] The Health Canada–produced monograph indicated that the genotype of alpha-Gal A determines the nature and extent of the clinical response to migalastat in FD patients. For amenable genotypes, the extent of the migalastat-induced accumulation of the alpha-Gal A protein can vary significantly. Therefore, response to migalastat can differ according to the specific amenable mutation. For non-amenable genotypes, migalastat may result in a net loss of alpha-Gal A activity, potentially worsening the disease condition. It also indicated that in clinical trials, individual response to migalastat treatment varied considerably among patients with amenable mutations and that patients should be assessed for treatment response or failure when initiating migalastat, and monitored periodically thereafter (every six months or more

frequently) throughout the treatment, and that the predictability of the extent of clinical outcome in amenable patients is limited.[5]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of migalastat 123 mg capsule (equivalent to 150 mg migalastat hydrochloride [HCl]) for long-term treatment of adults with a confirmed diagnosis of FD (deficiency of alpha-Gal A) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay.

Results and Interpretation

Included Studies

Two trials, ATTRACT and FACETS, met the inclusion criteria for this review. Both trials were phase III, multi-centre, randomized, controlled trials (RCTs). The ATTRACT trial was an active-controlled, randomized, open-label, multinational study that compared the efficacy and safety of migalastat with intravenous ERT (either agalsidase alfa or agalsidase beta) in patients with FD who were receiving ERT prior to study entry and who had migalastat-responsive GLA mutations. ATTRACT consisted of two periods, the first of which was an 18-month open-label treatment period in which patients were randomized 1.5:1 to switch from ERT to migalastat hydrochloride (150 mg once every other day; N = 36) or continue with ERT (N = 24). Randomization was stratified by gender and degree of proteinuria (low: < 100 mg/24 hours; high: ≥ 100 mg/24 hours). All patients who received treatment for 18 months were eligible to continue in a 12-month open-label extension (OLE) in which all patients received migalastat. The co-primary end points in the ATTRACT trial were annualized changes in renal function from baseline through month 18 assessed by measured and estimated glomerular filtration rate (mGFRiohexol and eGFRCKD-EPI).

The FACETS RCT was double-blind and compared migalastat with placebo over a six-month period in patients with FD and amenable mutations who had not previously received ERT within six months of eligibility screening. Patients were randomized in a 1:1 ratio to receive either oral migalastat HCl (150 mg) or matching placebo once every other day. Patients were stratified at randomization by gender. The primary end point compared the percentage of patients in the two treatment groups with a > 50% reduction from baseline to month 6 in the number of globotriaosylceramide (GL-3) inclusions per kidney interstitial capillary.

Key limitations in both trials were the sample size, no adjustment for multiple statistical testing, baseline imbalances in patient characteristics between the trial groups in both RCTs (which is of particular concern in trials with small participant numbers), and unbalanced attrition, reflecting uncertainty around the key outcomes. Furthermore, the clinical expert consulted for this review indicated that the key efficacy outcomes in the trials should have been hard clinical outcomes and not surrogates outcomes. In addition, in the ATTRACT trial, there was limited presentation of differences between the migalastat and ERT groups and no formal consideration of effect sizes; no justification was provided for the pre-specified criteria that defined comparability of glomerular filtration rate (GFR) results for migalastat and ERT; and the relevance of the value as an acceptable difference in the measured or estimated GFR (2.2 mL/min/1.73 m^2) over a period of 18 months is questionable. The FACETS trial had a short duration in the double-blind period and the clinical expert indicated that, with the exception of pain, the time is too short to draw any firm conclusions on most outcomes from the double-blind phase of the FACETS trial.

Efficacy

In the ATTRACT trial an analysis of a composite clinical outcome composed of renal, cardiac, and cerebrovascular events, or death, was conducted as a secondary efficacy end point. During the 18-month treatment period, the percentage of patients who had a renal, cardiac, or cerebrovascular event or died was 29% (10 of 34) of the patients switched from ERT to migalastat compared with 44% (8 of 18) of the patients who remained on ERT. The *P* value for the between-groups statistical comparison was 0.36, indicating no statistical significance between the treatment groups.[6] Overall, renal events were the most common, followed by cardiac events. No deaths occurred. The study was not powered to compare treatment groups for these clinical outcomes. The FACETS trial did not report event outcomes.

From the patient group input received by CADTH Common Drug Review (CDR) on this submission, patients consider improved quality of life, reduction in pain, and reduction in gastrointestinal problems to be important outcomes of treatment. Both ATTRACT and FACETS assessed health-related quality of life (HRQoL) using the Short-Form 36-Item Health Survey (SF-36) and pain using the Brief Pain Inventory (BPI) short form. In addition, FACETS employed the Gastrointestinal Symptoms Rating Scale (GSRS). In the ATTRACT trial, at baseline, the baseline SF-36 physical component summaries (PCS) and BPI scores indicated that patients in the migalastat treatment group had, on average, a higher level of functioning and less pain at study entry compared with the ERT group. These differences were greater than the general minimally important difference (MID) for the PCS, but it is unclear if the differences in the BPI scores are strong enough to have an influence on the interpretation of the effect estimates. The BPI pain severity component indicated that patients experienced only mild pain at baseline in the ATTRACT trial. Over the 18-month study period, mean scores for the SF-36 mental component summary (MCS) and PCS, 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. Also none of the change from baseline exceeded the MID of 2 points in the SF-36 PCS, 3 points in the SF-36 MCS and the MID of 1 point or 0.5 of its standard deviation (SD) for the BPI. No formal between-groups statistical comparison was undertaken in the SF-36 MCS and PCS, or the BPI. Changes in the SF-36 after 18/24 months of migalastat therapy in patients with amenable mutations were reported in the FACETS trial. Significant improvements were seen in the vitality (mean increase: 4.0) and general health (mean increase: 4.5) domains of the SF-36 from baseline. However, a claim of statistical significance cannot be made because there was no adjustment for multiple statistical testing; the values for the other health domains of the SF-36 appeared to remain stable over the 18/24 month period. No statistically significant differences between placebo and migalastat groups were observed from baseline to month 6 for the SF-36 and changes in BPI severity component scores. The GSRS was only measured in the FACETS trial. At six months, a greater percentage of patients receiving migalastat had an improvement in the diarrhea domain compared with placebo (38% versus 9%), and there was a statistically significant difference in scores for this domain between the two groups (−0.3 for migalastat versus 0.2 for placebo, $P < 0.05$). Changes in GSRS scores indicated a greater improvement in diarrhea and reflux symptoms in the migalastat group compared with the placebo group, but no difference between the groups for indigestion, constipation, or abdominal pain were reported. All results of HRQoL in the FACETS trial should be interpreted with caution because sample sizes were not reported, and no adjustment was made for multiplicity, and, due to the short duration of the double-blind period of the trial, it is not possible to draw any firm conclusions about effects of migalastat on HRQoL. In

addition, results from both trials on BPI indicate that migalastat does not have a beneficial effect on pain.

The pre-specified criteria for comparability of migalastat and ERT in the ATTRACT trial (a difference between the means for the annualized change in GFR for migalastat and ERT of no greater than 2.2 mL/min/1.73 m^2/year and 95% confidence intervals [CIs] for the means greater than 50% overlap) were met for both the co-primary measured GFR as assessed by plasma clearance of iohexol ($mGFR_{iohexol}$) and estimated GFR as assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ($eGFR_{CKD-EPI}$) outcomes in the modified intention-to-treat (mITT) population. However, mean annualized rates of change in $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ had wide confidence intervals, indicating uncertainty. Because the manufacturer did not provide the difference in mean annualized change between treatment groups or specify whether the 95% CIs for the means had greater than 50% overlap for the intention-to-treat (ITT) and per-protocol (PP) population, it is not possible to comment on whether or not the ITT and PP population meet the pre-specified criteria. In the ATTRACT trial, the 24-hour urine protein and albumin: creatinine ratio both increased but to a smaller extent in the migalastat group than the ERT group. The changes are uncertain.

Changes in renal function were evaluated as secondary end points in FACETS trial. 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),[7] indicating that patients may have had better stabilization of GFR in the placebo group than the migalastat group. However, six months may be too short a time to draw any conclusions about changes in renal function, especially given the sample sizes and large standard errors. No formal between-groups statistical comparison was undertaken for the measures of GFR. In the FACETS trial, the 24-hour urine protein increased in the migalastat group but decreased in the placebo group.

The primary outcome in the FACETS trial was the six-month change from baseline in the percentage of patients who had a ≥ 50% reduction in interstitial capillary globotriaosylceramide (GL-3) inclusions, analyzed in the ITT population. This was numerically higher in the migalastat group (40.6%; n = 34) than the placebo group (28.1%; n = 33), but the difference between groups was not statistically significant. Hence, the FACETS study did not meet its primary end point in the ITT population. A post hoc analysis at the end of the double-blind period (six months) was conducted in the patients with amenable mutations. The change from baseline analysis demonstrated that six months of treatment with migalastat was associated with a statistically significantly larger reduction in the average number of GL-3 inclusions per interstitial capillary compared with placebo: –0.250 ± 0.103 versus +0.071 ± 0.126, respectively; *P* = 0.008. There was no difference between migalastat and placebo in patients with non-amenable mutations. The European Medicines Agency Assessment Report for migalastat indicated that the GL-3 inclusions in renal tissue cannot be used for the prediction of the clinical benefit of migalastat because even though a qualitative correlation between GL-3 inclusions and clinical outcome can be assumed, a quantitative relation cannot be established.[8]

The ATTRACT trial only reported cardiac outcomes for mITT analyses, and these suggested that migalastat did not influence left ventricular ejection fraction (LVEF) but did improve left ventricular mass during the 18-month trial period. Left ventricular mass index (LVMI) decreased statistically significantly from baseline to 18 months in patients in the migalastat group (−6.6 g/m^2; 95% CI, −11.0 to −2.2); while in patients who continued on

ERT, the value at 18 months did not change from baseline (−2 g/m^2; 95% CI, −11.0 to 7.0). However, there is some uncertainty in these results, as the number of patients (33 in the migalastat group and 16 in the ERT group) included in this analysis was lower than the number specified in the mITT population (34 patients in the migalastat group and 18 patients in the ERT group) with no reason given for the missing data. Also, the patients in the ATTRACT study had relatively mild degrees of left ventricular hypertrophy (LVH) (baseline LVMI 95.3 g/m^2) and ATTRACT does not provide data on the effect of the drug in later stages of the cardiac disease (when fibrosis is more prominent). No formal between-groups statistical comparisons were undertaken for these outcome.

In the FACETS trial, no changes in LVMI were seen in the six-month double-blind period, which is expected due to the duration. Statistically significant reductions in LVMI from baseline were seen at 18 to 24 months of therapy in the FACETS trial.

In the open-label extension (OLE) of the ATTRACT and FACETS studies efficacy outcomes were similar to the main studies; no clear conclusions can be made regarding the long-term efficacy of migalastat in patients with FD due to the absence of comparator groups and the short duration of treatment.

Harms

In the ATTRACT trial, the majority of patients in both the migalastat and ERT groups (94% to 95%) experienced treatment-emergent adverse events (TEAEs). The most frequent adverse events were nasopharyngitis and headache, and these did not differ in frequency between the migalastat and ERT groups. In the FACETS trial, the majority of patients (91%) in both the migalastat and placebo groups experienced TEAE. The most frequent TEAEs were headache and nasopharyngitis, and these were both more frequent in the migalastat group (35% and 18% respectively) than in the placebo group (21% and 6%).

No deaths occurred in either of the trials or the OLE studies. In the ATTRACT trial, during the 18-month randomized treatment period, no patient discontinued treatment due to a TEAE. In the FACETS trial, no patient discontinued due to a TEAE in the migalastat group during the double-blind period (six months) and one patient (3%) discontinued due to a TEAE in the placebo group during the double-blind period (six months). Serious adverse events (SAEs) in ATTRACT were less frequent in the migalastat group than the ERT group (19% versus 33%). The most commonly occurring SAE was chronic heart failure deterioration, which occurred four times in one patient while receiving ERT. Chest pain occurred once in each of three patients receiving migalastat. Morbid obesity was reported in two patients receiving migalastat. In the ATTRACT OLE, 16 patients (31%) in the migalastat-migalastat group and three (20%) patients in the ERT-migalastat group experienced SAEs. In FACETS trial, the frequency of SAEs was lower in the migalastat group (6%), compared with the placebo group (12%). Only two patients in the migalastat group experienced SAEs during the double-blind period (six months); each patient experienced one SAE (post-procedural hematoma and hydronephrosis), both of which were assessed as unrelated to the study drug. In the FACETS OLE, SAEs were experienced by five (17%) and six (21%) of patients in the migalastat-migalastat and placebo-migalastat group, respectively. Migalastat was not associated with the infusion-associated reactions that commonly occur with ERT. Also, there was no risk of infections associated with vascular access because migalastat is an oral.

Potential Place in Therapy[a]

Prior to migalastat, ERT was the only pharmacological treatment option for patients with FD. ERT is a major advance in the treatment of patients with FD in that it can stabilize renal function and progressive increases in left ventricle size in many patients with this disorder. There are still many challenges in treating patients with FD. ERT requires regular biweekly intravenous infusions. While the manufacturers of ERT support patients to receive these infusions in their home, this is not available in all parts of the country and infusions remain an inconvenient and minimally invasive form of therapy. While most patients receive their infusions through a peripheral intravenous line, some patients over time lose peripheral intravenous access and will require insertion of a central venous catheter (CVC) with the attendant risks. An effective and well-tolerated oral medication such as migalastat would provide treatment that was more convenient for patients who tolerate ERT and would remove the need to insert a CVC in the small number of adult patients who require this.

Severe allergic reactions to ERT for FD are uncommon but there are a small number of patients with severe allergic reactions who either have to stop ERT or have to take premedications such as hydrocortisone, which have their own adverse effects. While an effective oral alternative would be very useful in patients who cannot tolerate ERT, it is unlikely that migalastat can fill that role in that the more severe infusion reactions often occur in patients with the more severe mutations (e.g., null mutations) and these mutations are not usually amenable to chaperone therapy. Thus, the issue of having an effective treatment alternative for patients who cannot tolerate ERT is likely to remain an unmet need even with the availability of migalastat. Due to the psychological impact of regular venepuncture in children with FD, it is more common to insert a CVC for ERT infusions, making effective oral therapy even more of an advantage in children than in adults. However, as migalastat is not indicated for children under the age of 18, this also will remain an unmet need. As migalastat is not indicated in patients with a GFR < 30 mL/min/1.73m^2, some patients with amenable mutations may not be able to use this oral option and will need to remain on ERT.

While ERT is beneficial in some of the disease manifestations of FD (e.g., renal, cardiac, gastrointestinal [GI]), it is not helpful with other manifestations, including some (e.g., pain, stroke) that have a major impact on patient quality of life. Also, some patients with ERT-responsive disease manifestations may continue to progress despite ERT. Hypotheses to explain such progression may include:

- Timing. If ERT is introduced at later stages of the disease, fibrosis (which is not ERT-responsive) rather than substrate accumulation (which is ERT-responsive) is the dominant pathological feature.
- Antibodies. Most males with FD will make antibodies to the ERT products. Unfortunately, as there is no international standardization of antibody assays, it is difficult to tease out what the effect of these antibodies might be on treatment response, although high-titre antibodies are associated with some adverse changes on surrogate biomarker profiles.
- Distribution. ERT does not cross into the brain and this may be related to its lack of efficacy on stroke, although the mechanisms of stroke in FD are not known.

There are likely other unknown factors that can influence response to ERT treatment. It is not clear how migalastat might affect these unmet needs. In terms of the disease

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

manifestations treatable with ERT, it is encouraging that left ventricular mass declined in the patients who were switched from ERT to migalastat. The authors hypothesize that this might be related to improved tissue penetration of the small molecule, but as the study was underpowered we cannot conclude that migalastat is superior to ERT. Also, the patients in the switch study had relatively mild degrees of LVH (baseline LVMI 96.5 g/cm^2) so ATTRACT does not provide data on what effect the drug might have in later stages of the cardiac disease (when fibrosis is more prominent). Data from the FACETS and ATTRACT trials suggest that migalastat does not have a beneficial effect on pain, although specific trials designed to answer this question have not been performed. Neither trial has had sufficient follow-up to look for an effect on stroke and as a result it is not clear if migalastat would be useful to reduce the risk of stroke in FD.

ERT is currently prescribed for FD patients who have established manifestations of the disease (i.e., in the secondary prevention setting) and is not currently recommended for patients who do not have evidence of disease involvement. Since 2006, all Canadian patients are followed through the CFDI, which provides funding for ERT (supported by the provinces) while collecting registry data to provide feedback to the payers on the outcomes of the Canadian patients. The ERT treatment guidelines undergo evidenced-based review on an annual basis and are available online (www.garrod.ca). The most recent version of the guidelines (2017) does include guidance on migalastat, and the indications for use and monitoring of migalastat therapy are similar to those for ERT. All Canadian patients have to be approved by a panel of five physicians before they are eligible for publicly funded treatment. Patients who do not meet the treatment guidelines are not approved for publicly funded therapy, although they would be eligible to receive it if they had private drug insurance. It is expected that migalastat, if available, would also be run through this same approval mechanism, at least as long as the CFDI continues to act on behalf of the provinces (Currently the contract for CFDI has been extended to September 2019.) If treatment approvals for migalastat are run through the CFDI, it would not be expected that the availability of the oral product would alter the number of patients eligible for treatment. A small number of patients (three in the first five years of the CFDI registry, as reported by Sirrs et al. Mol Genet Metab 2014) who are eligible for ERT decline this therapy. It is possible that some patients who decline ERT may accept an oral therapy if they have an amenable mutation. If so, the availability of an oral therapy may increase slightly the total number of patients who receive therapy in Canada. If the intention of the provinces is not to centralize migalastat prescriptions through the CFDI, then some other means to control prescribing should be in place, as the availability of an oral drug increases the number of physicians who might feel confident prescribing therapy, and given that the logistical issues around setting up ERT infusions are intimidating to physicians with limited experience. In Canada, immediately prior to instituting centralized control of ERT prescriptions through the CFDI, several patients who did not meet treatment criteria were started on ERT by non-expert physicians who were pressured to do so by the patients and the manufacturers. Without control over prescribing and with the availability of a well-tolerated oral agent, non-expert physicians may be pressured into considering treatment for patients who do not meet treatment guidelines, even though there are no data supporting the use of any type of treatment (ERT or oral) in the primary prevention setting.

The 2017 version of the CFDI guidelines made recommendations about the place in therapy for Canadian patients and these are available online at www.garrod.ca. Several issues are discussed in those guidelines for those with amenable mutations:

- The available data on migalastat as first-line therapy (FACETS) involve patients with relatively mild disease manifestations (baseline eGFR 94, baseline LVMI 93-101). If patients met Canadian treatment guidelines at this mild level of disease, it could be considered possibly as first-line therapy.
- The available data on switching from ERT to migalastat (ATTRACT) is also in patients with very mild disease (baseline Modification of Diet in Renal Disease eGFR 85, LVMI 95). In patients with disease stabilized at this level on ERT, switching could be considered.
- For patients with more significant disease manifestations, data on the effects of migalastat are lacking. It is possible that some clinicians might prefer to treat such patients for an interval of several years first with ERT (where the effects on disease parameters can be better predicted) before considering a switch, until more experience is available with migalastat in more advanced patients. The comfort level of physicians with using migalastat in this setting is likely to vary across the country.
  - The Canadian data at five years shows that patients newly started on ERT in Canada9 are more advanced (baseline eGFR 79 and LVMI 123) than the patients in the ATTRACT study.
- It is possible that migalastat might be the preferred initial treatment option in younger patients (even if they have more advanced disease then the FACETS cohort), but to avoid the deleterious psychological effects of biweekly intravenous enzyme infusions on a child, migalastat is not indicated for patients below the age of 18 at the current time.
- It is possible that some patients whose physicians feel they are appropriate candidates to switch to migalastat may be reluctant to do so as there is a high prevalence of anxiety and depression in the Fabry cohort and some patients may be anxious about changing therapy. This may change over time, as more patients in the country become familiar with the drug.

Monitoring of migalastat-treated patients is likely to be similar to that recommended for ERT. The manufacturer maintains a database of amenable mutations and evaluation of the mutation is required for all patients as part of the diagnostic process. If there was a novel mutation for which the utility of chaperone therapy was not known, then testing in the human embryonic kidney (HEK) cell line would be required. Presumably, this would be at the expense of the manufacturer. It is notable that the testing used to identify amenable mutations has evolved over time. As an example of this, the clinical trial of treatment-naive patients[10] included 17 patients who were originally thought to have amenable mutations and then were found with changes to the assay not to be amenable. This technology may continue to evolve over time (although no such changes to the assay are currently planned by the manufacturer) and it cannot be predicted how this might affect the number of patients potentially eligible for the oral therapy. If reclassification of amenability status of mutations occurs over time, it might not be apparent for two to four years that the drug is ineffective, as some manifestations (such as cardiac enlargement, which is a dominant feature of FD) are very slow to evolve. Increased monitoring of patients who have demonstrated long-term stability on ERT may be advisable after a switch to migalastat.

Conclusions

Two trials (ATTRACT and FACETS) met the inclusion criteria for this review. Both trials were phase III, multi-centre, RCTs that enrolled patients with FD who had migalastat-responsive GLA mutations. While the ATTRACT trial met the pre-specified criteria for demonstrating comparability of migalastat and ERT for the co-primary end points $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$, there is some uncertainty around the clinical effectiveness of migalastat compared with ERT because of the wide confidence intervals for the key efficacy outcomes,

as well as concerns related to the internal validity of the trial, including imbalances in the study group demographic characteristics and unbalanced attrition. The ATTRACT trial was a comparability trial, which should not be confused with, or considered as, an equivalence, non-inferiority, or superiority trial. The FACETS study did not meet its primary end point (changes in inclusions of GL-3 in interstitial capillary cells) in the ITT population. In both trials the effect of migalastat on clinically meaningful outcomes was uncertain, mainly because any observed effects on clinically meaningful outcomes (e.g., HRQoL, hard outcomes, and patient-reported symptoms) were marginal and limited by methodological considerations, including no between-group statistical testing and no detailed reporting of results. The safety profile of migalastat was similar to ERT and placebo in the controlled phase of the trials. While there were no apparent differences in safety results for migalastat between the controlled phases of the studies and the OLE, conclusions regarding the long-term safety of migalastat in patients with FD are limited due to the absence of a comparator group and the short duration of treatment.

Table 1: Summary of Results

Outcome	ATTRACT		FACETS	
	Migalastat	ERT	Migalastat	Placebo
Renal, cardiac, or cerebrovascular events, or death				
Renal, N (%)	8 (24)	6 (33)	NR	NR
Cardiac, N (%)	2 (6)	3 (17)	NR	NR
Cerebrovascular, N (%)	0 (0)	1 (6)	NR	NR
Death, N (%)	0 (0)	0 (0)	NR	NR
Any, N (%)	10 (29)	8 (44)	NR	NR
SF-36v2				
Physical component				
Baseline, mean ± SEM	47.8 ± 1.9	40.4 ± 2.7	NR	NR
Change from baseline to month 18, mean (95% CI)	0.96 (−1.0 to 2.9)	−1.92 (−6.7 to 2.8)	NR	NR
Treatment difference	NR		NR[a]	
Mental component			NR	NR
Baseline, mean ± SEM	49.3 ± 1.8	50.6 ± 2.6	NR	NR
Change from baseline to month 18, mean (95% CI)	0.08 (−3.3 to 3.4)	−0.41 (−4.3 to 3.5)	NR	NR
Treatment difference	NR		NR[a]	
BPI-SF (pain severity)				
Baseline, mean ± SEM	1.29 ± 0.31	2.12 ± 0.56	NR	NR
Change from baseline to month 18, mean (95% CI)	0.15 (−0.56 to 0.88)	−0.19 (−0.98 to 0.59)	NR	NR
Treatment difference	NR		NR[a]	
Changes in Gastrointestinal Symptoms Rating Scale				
Diarrhea				
Mean baseline values (n)	NR	NR	2.3 (28)	2.1 (22)
Change from baseline to month 6 (Double-blind period)	NR	NR	−0.3[b]	0.2
Reflux				
Mean baseline values (n)	NR	NR	1.4 (28)	1.4 (22)
Change from baseline to month 6, double-blind period	NR	NR	−0.1	0.2

Outcome	ATTRACT		FACETS	
	Migalastat	ERT	Migalastat	Placebo
Indigestion				
Mean baseline values (n)	NR	NR	2.5 (28)	2.4 (22)
Change from baseline to month 6, double-blind period	NR	NR	−0.1	−0.1
Constipation				
Mean baseline values (n)	NR	NR	1.9 (28)	2.0 (22)
Change from baseline to month 6, double-blind period	NR	NR	0.1	0.2
Abdominal pain				
Mean baseline values (n)	NR	NR	2.1 (28)	2.3 (22)
Change from baseline to month 6, double-blind period	NR	NR	0	0
Patients with > 0 AEs				
N (%)	34 (94)	20 (95)	31 (91)	30 (91)
SAEs				
(%)	19%	33%	2 (6)	4 (12)
WDAEs				
N (%)	0	0	0	1 (3)
Number of deaths				
(%)	0	0	0	0

AE = adverse event; BPI-SF = Brief Pain Inventory Short Form-Pain severity component; CI = confidence interval; ERT = enzyme replacement therapy; NR = not reported; SAE = serious adverse event; SEM = standard error of the mean; SF-36v2 = Short Form 36-Item Health Survey version 2; WDAE = withdrawal due to adverse event.

[a] In the FACETS trial, for both SF-36 and BPI-SF, no statistically significant differences between placebo and migalastat groups were observed from baseline to month 6; neither of the two PROs demonstrated worsening on migalastat between six and 24 months.

[b] $P = 0.03$ using ANCOVA.

Introduction

Disease Prevalence and Incidence

Fabry disease (FD), also called Anderson-Fabry disease, is an X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal alpha-galactosidase A (alpha-Gal A) activity, resulting in the accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in lysosomes in cells throughout the body.[1-3] Beginning early in life, this accumulation progressively affects organ function, leading to the serious and life-limiting sequelae of the disease, including neuropathic pain; skin disorders; progressive and severe renal impairment; pulmonary manifestations; cardiac problems including arrhythmia and cardiomyopathy; central nervous system involvement including cerebrovascular events; and early mortality.[1] Consequently, FD has a devastating effect on both quality and length of life, as patients deal with the variety of systemic symptoms and progressive organ damage.

Patients state that FD significantly affects their physical and emotional well-being along with severely affecting their ability to perform daily activities. Severe, sharp, or excruciating pain and swelling, particularly in the hands and feet, is often proclaimed to be the most bothersome symptom. Patients are also often intolerant to heat and cold. Symptoms such as fatigue and lack of energy significantly affect patients' abilities to perform daily activities.

FD is the second most common lysosomal storage disorder, after Gaucher's disease.[2] The manufacturer for the drug under review (Amicus Therapeutics) commissioned a report from the Canadian Fabry Disease Initiative (CFDI) in September of 2016, which provided data on the 404 FD patients participating in the registry.[4] This number is understood to represent a significant proportion of the total number of identified FD patients in Canada,[11] and a prevalence of approximately 0.88 per 100,000. A specific mutation, c.427G>C, known as the Nova Scotia mutation, has an elevated prevalence in Canada,[11] and 91 of the 424 identified Canadian FD patients reside in the province of Nova Scotia.[4] The manufacturer indicated that as of March 2017, data obtained from the CFDI suggests that there are currently 424 Fabry disease patients in Canada, of whom 90 (21.2%) have been identified as having mutations amenable to treatment with migalastat. Of these, 44 currently receive enzyme replacement therapy (ERT) and are over the age of 16 years.[4] The manufacturer indicated that of the 90 patients who have an amenable mutation, 28 reside in Alberta, 16 in British Columbia, five in Manitoba, two in Nova Scotia, 27 in Ontario, eight in Québec, three in Saskatchewan, one in Yukon, and none in the provinces of New Brunswick, Newfoundland, and Prince Edward Island.

Standards of Therapy

There is no cure for FD.[12] Treatment for FD consists of supportive care through a multidisciplinary approach to the management of symptoms and risk factors, and specific treatment in the form of enzyme replacement therapy (ERT).[3]

The 2016 Canadian Fabry Disease Treatment Guidelines recommend that ERT should be considered in all patients with documented FD, of any sex or age, when there are manifestations for which ERT is of proven benefit.[3] The guidelines identify several potential benefits of ERT, including stabilization of renal function, as measured by glomerular

filtration rate (GFR) decline and proteinuria, stabilization of Fabry-related cardiomyopathy as measured by stable or declining left ventricular mass index (LVMI), left ventricular wall thickness and normalization of the heart's PR interval, and improvement of gastrointestinal symptoms such as diarrhea, abdominal cramps, pain, nausea, vomiting, and heartburn. Conversely, tachycardia, bradycardia, stroke or transient ischemic attack, proteinuria, hearing loss, and depression are characteristic symptoms of FD, for which the effectiveness of ERT has not been demonstrated. There are potential risks of ERT, such as development of infusion reactions to ERT, which take the form of chills, edema, fever, rash, nausea, and dyspnea. Anti-agalsidase antibodies may be the cause of such infusion reactions in some cases.[3]

Currently two commercially marketed drugs represent the range of ERT for FD in Canada: Replagal (agalsidase alfa)[13] and Fabrazyme (agalsidase beta).[14] The 2016 Canadian Fabry Disease Treatment Guidelines indicated that the outcomes of agalsidase alfa and agalsidase beta therapy are equivalent and that, "given the lack of data to support alternative dose and dosing and possible risks associated with a switch, considerations of changing drug, dose, or dosing are best done in the setting of a formal clinical trial."[3] In the updated 2017 Canadian Fabry Disease Treatment Guidelines, ERT is recommended for all patients who are 18 years of age or older and meet one or more indications for disease-specific therapy.[15] Chaperone therapy is recommended for patients who are 18 years of age or older, who meet at least one indication for disease-specific therapy, and who have a mutation amenable to chaperone therapy, are not considering pregnancy, and have no contraindication to chaperone therapy.[15]

Patients' noted an improvement in their symptoms on ERT, including organ protection, increased energy, ability to work (or return to work), socialize, and carry out daily activities, and a reduction in pain in their extremities. However, some patients also noted that they continued to experience symptoms related to their FD. Patients often described the infusion treatment for ERT as cumbersome and problematic, as infusion centres (often far away from patients) and the times associated with the actual infusions significantly affect their lives.

Drug

Migalastat has a Health Canada–approved indication for long-term treatment of adults with a confirmed diagnosis of FD (deficiency of alpha-Gal A) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay.[5] The Health Canada–recommended dose in adults 18 years and older is 123 mg of migalastat (1 capsule) once every other day at the same time of day.[5] Galafold is available as a hard capsule containing 123 mg of migalastat (equivalent to 150 mg of migalastat hydrochloride [HCl]).[5]

Preclinical in vitro and in vivo studies have demonstrated that migalastat acts as a pharmacological chaperone, selectively and reversibly binding, with high affinity, to the active site of wild-type alpha-Gal A and specific mutant forms of alpha-Gal A.[16] The genotypes of these specific mutant forms are referred to as amenable mutations. Migalastat is a specific, potent, reversible, competitive inhibitor of human alpha-Gal A. It is also a specific structural stabilizer for the wild type and many mutant forms of alpha-Gal A. The net biochemical and clinical effects of migalastat in FD patients initially involves intracellular accumulation of migalastat-stabilized and inhibited alpha-Gal A enzyme, followed by the recovery of activity of accumulated alpha-Gal A after migalastat drops to a sub-inhibitory level due to pharmacokinetic elimination. The efficacy of migalastat depends on a net

increase of alpha-Gal A activity resulting from a sufficiently high level of accumulation of the migalastat-inhibited enzyme and an adequate duration for recovery of enzyme activity during the dosing interval. The genotype of alpha-Gal A determines the nature and extent of the clinical response to migalastat in FD patients. For amenable genotypes, the extent of the migalastat-induced accumulation of the alpha-Gal A protein can vary significantly, and response to migalastat can differ according to the specific amenable mutation. The Health Canada–approved product monograph for migalastat indicated that, for non-amenable genotypes, migalastat may result in a net loss of alpha-Gal A activity, potentially worsening the disease condition. It also mentioned that in clinical trials, individual response to migalastat treatment varied considerably among patients with amenable mutations, and that patients should be assessed for treatment response or failure when initiating migalastat, and monitored periodically thereafter (every six months or more frequently) throughout the treatment.[5]

For the purposes of treatment with the chaperone therapy migalastat, GLA mutations are generally classified into types of mutations that are either “responsive” or amenable” and those that are “non-responsive” or “non-amenable” to treatment with migalastat.[17,18] See Appendix 7: Summary of GLA Mutational Assay for more information regarding the mutations and the mutational assay that is used to assess whether patients with FD have amenable mutations to oral migalastat. Amenability status is determined by the results of the genetic test that is required for the diagnosis of FD. When the results of the mutational analysis are made available, the treating physician is able to determine if a patient has an amenable mutation by consulting the amenability table in the product monograph. According to the clinical expert consulted for this review, a European amenability table is available online, and a Canadian version is expected to become available.

In addition to migalastat, two other agents (agalsidase alfa and agalsidase beta) are currently approved in Canada for the treatment of patients with a confirmed diagnosis of FD (Table 2).

Table 2: Key Characteristics of Migalastat, Agalsidase alpha, and Agalsidase beta

	Migalastat (Galafold)	Agalsidase alfa (Replagal)	Agalsidase beta (Fabrazyme)
Mechanism of Action	Stabilize and inhibit amenable mutant forms of alpha-Gal A enzyme	Catalyze the hydrolysis of Gb3, cleaving a terminal galactose residue from the molecule	Catalyze the hydrolysis of glycosphingolipids, including GL-3, in the lysosomes of multiple cell types and tissues
Indication[a]	Long-term treatment of adults with a confirmed diagnosis of FD and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay	Long-term ERT in patients with a confirmed diagnosis of FD	Long-term ERT in patients with a confirmed diagnosis of FD
Route of Administration	Oral	IV	IV
Recommended Dose	123 mg capsule once every other day at the same time of day	0.2 mg/kg body weight every other week by IV infusion over 40 minutes.	1.0 mg/kg body weight infused every 2 weeks as an IV infusion
Serious Side Effects / Safety Issues		• Idiosyncratic infusion-related reactions • Develop antibodies to the protein	• Anaphylaxis and allergic reactions • Infusion reactions • Develop immunoglobulin G antibodies
Other	• Should not be used in patients with non-amenable mutations • Should not be used concomitantly with ERT • Should not be used in patients with severe renal insufficiency		

ERT = enzyme replacement therapy; FD = Fabry disease; Gb3 = globotriaosylceramide; GL-3 = globotriaosylceramide; IV = intravenous.
[a] Health Canada indication.
Source: Product monographs.[5,13,14]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of migalastat 123 mg capsule for long-term treatment of adults with a confirmed diagnosis of FD (deficiency of alpha-Gal A) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult with a confirmed diagnosis of Fabry disease (deficiency of alpha-Gal A) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay • ERT-experienced patients • ERT-naive patients • Patients with early stages of the disease • Patients with advanced stages of the disease (patients with impairment of body systems such as kidney, heart, etc.) • Organ systems involved • Patients with mutations associated with classic phenotype • Gender
Intervention	Migalastat 123 mg (1 capsule) once every other day at the same time of day
Comparators	Agalsidase alfa Agalsidase beta Placebo
Outcomes	**Key efficacy outcomes:** • Composite outcome of: death, cardiovascular events, cerebrovascular events, or renal events • Incidence of hospitalization • Health-related quality of life[a] • Patient-reported symptoms (improvement in pain measured by any valid method, improvement in gastrointestinal symptoms)[a] **Other efficacy outcomes:** • Change in renal functions • Change in cardiac function • Nerve fibre conduction • Neuropathic pain • Tolerance to cold and heat[a] • Exercise tolerance[a] • Change in incidence of cerebrovascular events • Change in accumulation of enzyme alpha-Gal A, Gb3 and plasma lyso-Gb3 **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms/harms of special interest (infusion reactions)
Study Design	Published and unpublished phase III RCTs

AE = adverse event; alpha-Gal A = alpha-galactosidase A; ERT = enzyme replacement therapy; Gb3 = globotriaosylceramide; lyso-Gb3 = globotriaosylsphingosine; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Outcomes identified as important based on patient input.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was migalastat (Galafold).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on July 13, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on December 12, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug regulatory approvals, advisories and warnings, drug class reviews, clinical trial registries, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

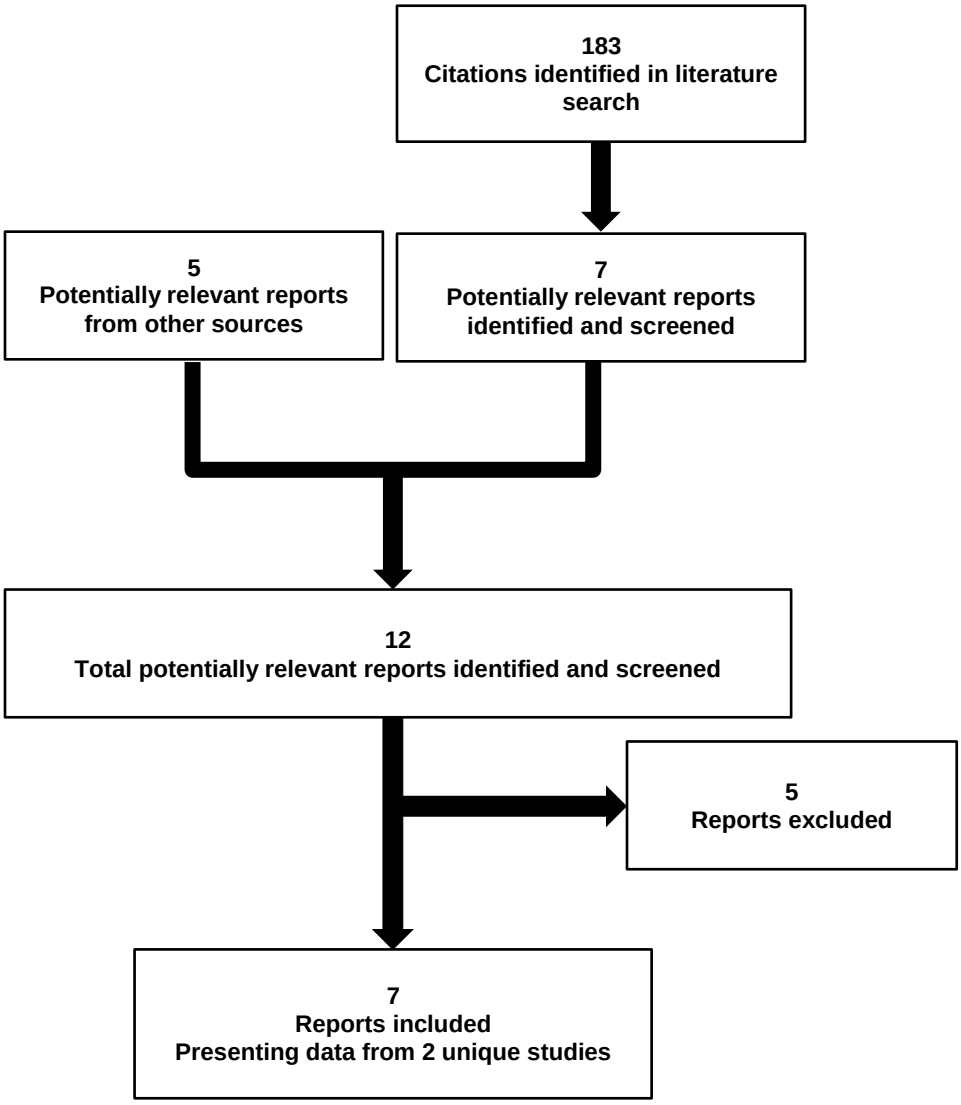

Table 4: Details of Included Studies

		ATTRACT	FACETS
Designs & Populations	**Study Design**	OL, active-controlled, phase III RCT	DB placebo-controlled, phase III RCT
	Locations	25 study centres in Australia, Austria, Belgium, Brazil, Denmark, France, Italy, Japan, the UK, and the US	36 study centres in Argentina, Australia, Belgium, Brazil, Canada, Denmark, Egypt, France, Germany, Italy, Netherlands, Poland, Spain, Turkey, the UK, and the US
	Randomized (N)	60	67
	Inclusion Criteria	• Male or female, diagnosed with Fabry disease and between 16 and 74 years of age, inclusive • Confirmed GLA mutation shown to be responsive to migalastat in the HEK assay • GFR ≥ 30 mL/min/1.73 m^2 • Initiated treatment with ERT at least 12 months before visit 2 • Patients taking ACEIs or ARBs must have been on a stable dose for a minimum of four weeks before visit 1	• Male or female between the ages of 16 and 74, inclusive, diagnosed with Fabry disease • Naive to ERT or had not received ERT for at least the six months before screening • A confirmed GLA mutation that had been shown to be responsive to migalastat in the HEK assay • Urine GL-3 ≥ 4 times the ULN at screening • Patients taking ACEIs or ARBs must have been on a stable dose for a minimum of four weeks before baseline
	Exclusion Criteria	• Underwent, or scheduled to undergo, kidney transplantation or any other solid organ • Transplantation • Was on regular dialysis that was specifically for the treatment of chronic kidney disease • Had a documented transient ischemic attack, stroke, unstable angina, or myocardial infarction within the three months before visit 1 • Had clinically significant unstable cardiac disease in the opinion of the investigator	• Patient had undergone or was scheduled to undergo kidney transplantation, or was currently on dialysis • eGFR < 30 mL/min/1.73m^2 (CKD stage 4 or 5) based on MDRD equation (eGFRMDRD) at screening
Drugs	**Intervention**	150 mg migalastat HCl q.o.d.	150 mg migalastat HCl q.o.d
	Comparator(s)	ERT (agalsidase alfa or agalsidase beta)[a]	Matching placebo
Duration	**Phase**		
	Screening/baseline period	Approximately 2 months	Up to 2 months (stage 1)
	Double-blind	--	6 months (Stage 1)
	Open-label	18 months	6 months (stage 2)
	Open-label extension period	12 months	12 months
Out comes	**Primary End Point**	Annualized change in $mGFR_{iohexol}$ and $eGFR_{CKD-EPI}$ from baseline through month 18	Proportion of patients with a ≥ 50% reduction from baseline to month 6 in the average number of GL-3 inclusions per IC
	Other End Points	• Composite end point (based on renal, cardiac, cerebrovascular events and death) • SF-36 v2 • BPI	• SF-36 v2 • BPI • GSRS

		ATTRACT	FACETS
		• LVMI • LVPWT • IVSWT • Urine GL-3 • 24-hour urine protein, albumin, and creatinine • Change from Baseline in mGFRiohexol • Change from Baseline in eGFRCKD-EPI • Change from Baseline in eGFRMDRD • Change in plasma lyso-GL-3 from baseline • Safety	• Per cent change from baseline in GL-3 inclusions per IC • Per cent ICs with zero GL-3 inclusions • Cardiac function (left ventricular mass, septal wall thickness, fractional shortening and ejection fraction as assessed by echocardiography) • Urine GL-3 • mGFRiohexol • eGFR • 24-hour urine protein, albumin, and creatinine • WBC alpha-Gal A activity • Plasma lyso-Gb3 • Safety
NOTES	**Publications**	Hughes et al.[6]	Germain et al.[10]

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; BPI = Brief Pain Inventory; CKD = chronic kidney disease; DB = double-blind; eGFR = estimated glomerular filtration rate; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate as measured by the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = estimated glomerular filtration rate as measured by the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GL-3 = globotriaosylceramide, also referred to as Gb3 or ceramide trihexoside; GLA = alpha-galactosidase A; GSRS = Gastrointestinal Symptoms Rating Scale; HCl = hydrochloride; HEK = human embryonic kidney-293; IC = kidney interstitial capillary; IVSWT = intraventricular septal wall thickness; LVMI = left ventricular mass index; LVPMT = left ventricular posterior wall thickness; lyso-Gb3 = globotriaosylsphingosine; MDRD = Modification of Diet in Renal Disease; $mGFR_{iohexol}$ = measured glomerular filtration rate as assessed by plasma clearance of iohexol; NICE = National Institute for Health and Care Excellence; OL = open-label; q.o.d. = every other day; RCT = randomized controlled trial; SF-36 = Short-Form Health Survey; WBC = white blood cell; ULN = upper limit of normal.

[a] Throughout the course of the screening period and 18-month randomized treatment period, commercially available agalsidase for intravenous infusions was prescribed by the patient's treating physician and was administered in accordance with the approved prescribing information. All patients were to continue ERT during the screening period; patients were to be given ≥ 80% of the currently labelled dose and regimen during the screening period. Patients randomized to the ERT group were to continue to receive at least 80% of the currently labelled dose and regimen during the 18-month randomized treatment period.

Note: Three additional reports were included: CDR submission,[4] NICE Migalastat for treating Fabry disease evaluation report,[7] and the European Medicines Association Report.[8]

Sources: Hughes et al.,[6] Germain et al.,[10] Clinical Study Reports.[19,20]

Included Studies

Description of Studies

Two trials, ATTRACT and FACETS, met the inclusion criteria for this review. Both trials were phase III, multi-centre, RCTs.

The ATTRACT trial was an active-controlled, randomized, open-label, multinational study that compared the efficacy and safety of migalastat to intravenous ERT (either agalsidase alfa or agalsidase beta) in patients with FD who were receiving ERT prior to study entry and who had migalastat-responsive (amenable) GLA mutations. ATTRACT consisted of two periods, the first of which was an 18-month open-label treatment period in which patients were randomized 1.5:1 to switch from ERT to migalastat hydrochloride (HCl) (150 mg once every other day) or continue with ERT. Randomization was stratified by gender and degree of proteinuria (low: < 100 mg/24 hours; high: ≥ 100 g/24 hours). Patients were randomized to treatments by interactive voice response system. All patients who received treatment for 18 months were eligible to continue in a 12-month open-label extension (OLE) in which all patients received migalastat.

The FACETS trial was a placebo-controlled, double-blind trial that evaluated the efficacy and safety of migalastat in patients with FD and with amenable mutations who were ERT-naive (had either never received ERT or had not received ERT for at least six months prior to screening). FACETS consisted of two stages and a 12-month OLE. Stage 1 consisted of a screening period (up to two months) and a six-month, double-blind, randomized, placebo-controlled treatment period. Patients were randomized in a 1:1 ratio to receive either oral migalastat HCl (150 mg) or matching placebo once every other day. Patients were stratified at randomization by gender. Patients were allocated to treatments using a central interactive voice randomization system. All patients who completed stage 1 were eligible to continue in a six-month open-label period in which all patients received migalastat (stage 2). This was followed by a 12-month OLE.

Populations

Inclusion and Exclusion Criteria

The ATTRACT and FACETS studies both enrolled patients diagnosed with FD between 16 and 74 years of age, inclusive, with a confirmed GLA mutation responsive to migalastat in the human embryonic kidney (HEK) assay. The main difference between the inclusion and exclusion criteria of the two studies was that FACETS patients were required to be naive to ERT or had not received ERT for at least the six months before screening while patients in ATTRACT had to have been receiving ERT for at least 12 months. Patients were excluded from the trials if they had undergone or were scheduled to undergo kidney transplantation, or were currently on dialysis. Patients were also excluded if their GFR was less than 30 mL/min/1.73 m^2.

Baseline Characteristics

In both trials, baseline characteristics were reported for the safety population, which included all randomized patients who received at least one dose of study drug.

In the ATTRACT study, a total of 60 patients were randomized, of which four were considered post hoc as having a non-amenable GLA mutation. Fifty-seven patients were included in the safety population. Thirty-six patients were randomized to migalastat (16 males and 20 females; mean age of 50.5 years), and 21 were randomized to continue ERT (nine male and 12 female patients; mean age of 46.3 years). Thirty-seven of the 57 (65%) were receiving agalsidase alpha at baseline. Of the 57 patients randomized, a total of 27 of patients were receiving angiotensin-converting enzyme inhibitors (ACEIs), an angiotensin receptor blocker (ARB) or renin inhibitors (RIs). In the FACETS trial, 34 patients were randomized to migalastat (12 males and 22 females; mean age of 40.0 years) in stage 1, and 33 were randomized to receive placebo (12 males and 21 females; mean age of 44.5 years). Of the 34 patients randomized to migalastat, 28 (82%) had an amenable GLA mutation, versus 22 (67%) in the placebo treatment group (Table 5). In both trials a new validated HEK assay was used for the determination of amenability of the mutant alpha-Gal A forms that became available during the trials. Consequently, some patients who were initially classified as having an amenable mutation were subsequently identified as having a non-amenable mutation.

In each trial, there were some imbalances in the patients' baseline characteristics between the migalastat and comparator groups, as can be seen in Table 5. In both trials, the mean age of patients differed between the treatment groups. The mean age for patients in the ATTRACT study was four years older in the migalastat group than the ERT group, while in FACETS the average age was five years younger in the migalastat group than the placebo

group. In the FACETS trial, the proportion of patients who had an amenable GLA mutation was 15% higher in the migalastat group than the placebo group. In both trials, patients in the migalastat treatment groups had a shorter time since diagnosis than those in the comparator group, especially in the ATTRACT trial, in which the median time since diagnosis was double in the ERT group (9.4 years) compared with the migalastat treatment group (4.5 years). For both trials, the mean total urine protein collected over 24 hours was less in the migalastat treatment groups than in the comparator group. In the FACETS trial, a lower proportion of patients had received an ACEI, ARB or RI (18% versus 39%) and a lower proportion of patients in the migalastat group than the placebo group had received prior ERT (15% versus 36%). The baseline Short-Form 36-Item Health Survey (SF-36) physical component score (PCS) in the ATTRACT trial indicated that patients in the migalastat treatment group had, on average, a higher level of functioning at study entry compared with the ERT group.

In the ATTRACT trial, 50 out of 56 randomized patients with amenable mutations had more than two organ systems involved at the start of the trial (Table 6). While of the patients included in the FACETS trial, 47 (94%) out of 50 patients with amenable mutations had more than two organ systems involved at the start of the trial (Table 6 and Table 7).

Table 5: Summary of Baseline Characteristics (Safety Population)

	ATTRACT		FACETS	
	Migalastat n = 36	**ERT n = 21**	**Migalastat n = 34**	**Placebo n = 33**
Age (years)				
Mean ± SEM	50.5 ± 2.3	46.3 ± 3.3	40.0 (13.29)[a]	44.5 (10.18)[a]
Median (min, max)	54.0 (18, 70)	48.0 (18, 72)	37.0 (16, 68)	46.0 (24, 64)
Sex, n (%)				
Male	16 (44)	9 (43)	12 (35)	12 (36)
Female	20 (56)	12 (57)	22 (65)	21 (64)
Years since diagnosis, mean (SD)	10.2 (11.76)	13.4 (12.47)	5.7 (6.76)	7.1 (7.84)
Median	4.5	9.4	4.1	5.0
Min, max	1, 43	1, 39	0, 34	0, 34
24-hour protein (mg/24 hours), mean (SD)	267 (411.15)	360 (693.27)	342 ± SEM (79)	452 ± SEM (109)
Median	129	108	NR	NR
IQR	393	483	NR	NR
Min, max	0, 2282	0, 3154	NR	NR
$mGFR_{iohexol}$ (mL/min/1.73 m^2)				
Mean ± SEM	82.4 ± 3.0	83.6 ± 5.2	83 ± 5.3	86 ± 4.3
SD	18.105	23.938	NR	NR
Median	81.30	85.10	NR	NR
Min, max	51.7, 124.0	33.0, 132.2	NR	NR
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)				
Mean ± SEM	89.6 ± 3.7	95.8 ± 4.1	95.4 ± 4.9	93.8 ± 3.7
SD	22.198	19.202	28.51	20.64
Median	85.914	96.84	97.4	98.1
Min, max	51.33, 145.12	44.83, 129.52	41, 164	45, 127
$eGFR_{MDRD}$ (mL/min/1.73 m^2, mean ± SEM)	83.6 ± 3.7	87.8 ± 19.0	90 ± 4.0	88 ± 6.5

	ATTRACT		FACETS	
	Migalastat n = 36	ERT n = 21	Migalastat n = 34	Placebo n = 33
Left ventricular mass index (g/m^2)	97.5 ± 4.7	94.6 ± 5.6	NR	NR
Prior ERT, n (%)	35 (97.2)	21 (100)	5 (15)	12 (36)
Agalsidase beta	11 (31)	8 (38)	NR	NR
Agalsidase alfa	24 (67)	13 (62)	NR	NR
Use of ACEI/ARB/RI, n (%)	16 (44)	11 (52)	6 (18)	13 (39)
Amenable GLA mutation, n (%)	34 (94)	19 (90)	28 (82)	22 (67)
Proteinuria > 100 mg/24 h, n (%)	21 (58)	12 (57)		
Proteinuria > 150 mg/24 h	NR	NR	20 (59)	24 (73)
Proteinuria > 300 mg/24 h	NR	NR	9 (26)	13 (39)
Proteinuria > 1,000 mg/24 h	NR	NR	3 (9)	3 (9)
Urine albumin: creatinine ratio (mg/mmol), n	35	20	33	33
mean (SD)	13.4	18.8	18.83 (36.404)	26.71 (47.259)
SF-36v2 physical component score, baseline (mean ± SEM)	47.8 ± 1.9	40.4 ± 2.7	NR	NR
SF-36v2 Mental component score, baseline (mean ± SEM)	49.3 ± 1.8	50.6 ± 2.6	NR	NR

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; $eGFR_{CKD\text{-}EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; NR = not reported; RI = renin inhibitor; SF-36v2 = Short Form-36 Health Survey version 2; SD = standard deviation; SEM = standard error of mean.

[a] Results in (parentheses) are for standard deviation.

Sources: Hughes et al.[6]; Germain et al.[10]; Clinical Study Reports[19,20]; Amicus Therapeutics[21]; NICE Migalastat for treating Fabry disease evaluation report[7]; the European Medicines Association Report.[8]

Table 6: Baseline Assessment of Disease Severity by Sex

	ATTRACT (Randomized Patients With Amenable Mutations)		FACETS (Amenable Mutations)	
Parameter, n/N (%)	**Males**	**Females**	**Males**	**Females**
Fabry disease in ≥ 2 organ systems	21/23 (87)	29/33 (88)	18/18 (100)	29/32 (91)
Angiokeratoma or corneal whorling	13/23 (57)	16/33 (48)	12/18 (61)	13/32 (41)
Cardiac events	15/23 (65)	25/33 (75)	15/18 (83)	11/32 (35)
CNS events	17/23 (74)	12/33 (36)	11/18 (66)	16/32 (50)
Neuropathic P\pain	14/23 (61)	22/33 (67)	13/18 (72)	25/32 (78)
Renal impairment	17/23 (74)	25/33 (76)	18/18 (100)	27/32 (84)
Gastrointestinal symptoms	14/23 (61)	20/33 (61)	10/18 (56)	18/32 (56)
Plasma lyso-Gb3	NR	NR	10/11 (91)	19/20 (94)
WBC alpha-Gal A activity (vs. normal)				
< 1%	NR	NA	7/16 (44)	NA
< 3%	NR	NA	14/16 (87)	NA

Alpha-Gal A = alpha-galactosidase A; CNS = central nervous system; lyso-Gb3 = globotriaosylceramide; NA = not applicable; NR = not reported; WBC = white blood cell; vs. = versus.
Source: Hughes et al.[6] and Germain et al.[10]

Table 7: Baseline Assessment of Disease Severity by Treatment Group and Sex in FACETS Trial (Amenable Mutations)[a]

	Migalastat		Placebo	
Parameter, n/N (%)	**Males**	**Females**	**Males**	**Females**
Fabry disease in ≥ 2 organ systems	9/9 (100)	18/19 (95)	9/9 (100)	11/13 (85)
Plasma lyso-Gb3	4/5 (80)	12/13 (92)	5/6 (83)	7/7 (100)
WBC alpha-Gal A activity (vs. normal)				
< 1%	4/7 (57)	NA	3/9 (33)	NA
<3%	6/7 (86)	NA	6/9 (67)	NA

Alpha-Gal A = alpha-galactosidase A; lyso-Gb3 = globotriaosylceramide; NA = not applicable; WBC = white blood cell; vs. = versus.
[a] No data were available for the ATTRACT trial.
Source: Germain et al.[10]

Interventions

In the ATTRACT trial, patients were randomized 1.5:1 to either stop ERT treatment and start treatment with migalastat HCl (150 mg capsule) orally once every other day at approximately the same time, or to continue with ERT (agalsidase alfa or agalsidase beta). Randomization was stratified by gender and degree of proteinuria (low: < 100 mg/24 hours; high: ≥ 100 mg/24 hours). Throughout the course of the screening period and 18-month randomized treatment period, commercially available agalsidase for intravenous infusions was prescribed by the patient's treating physician and was administered in accordance with the approved prescribing information. All patients were to continue ERT during the screening period; patients were to be given at least 80% of the labelled dose and regimen during the screening period. Patients randomized to the ERT group were to continue to receive at least 80% of the labelled dose and regimen during the 18-month randomized treatment period. During the OLE period, patients who received migalastat during the 18-month randomized treatment period continued receiving migalastat. All patients in the ERT group during the 18-month randomized treatment period discontinued ERT and started treatment with migalastat at entry into the OLE period. During the OLE period, all patients took one migalastat HCl (150 mg) capsule orally once every other day at approximately the same time and inactive reminder capsules on alternating days. Patients taking ACEIs or ARBs must have been on a stable dose for at least one month before visit 1. Use of any investigational or experimental therapy, miglitol, or miglustat was prohibited while on study.

In the FACETS trial, patients were randomized in a 1:1 ratio to receive either oral migalastat HCl (150 mg capsule) or placebo capsules that were identical in appearance to the migalastat capsules. Patients were stratified at randomization by gender. Patients took either one capsule of 150 mg migalastat HCl or placebo once every other day, at approximately the same time of day. Patents were required to fast two hours before and two hours after taking each dose of study medication. During the double-blind treatment period (stage 1), all patients, investigators, and the sponsor were blinded to treatment assignments. During the open-label treatment period (stage 2), patients and investigators remained blind to treatment assignments from stage 1. Use of ACEIs or ARBs during the four weeks before the baseline visit was documented in the case report form. Use of the following medications was prohibited within six months of the screening visit and at any time throughout the study: agalsidase beta, agalsidase alfa, miglitol, miglustat, and any investigational or experimental therapy.

Outcomes

In the ATTRACT trial, the co-primary end points were:

- Annualized changes from baseline through month 18 in estimated GFR (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ($eGFR_{CKD-EPI}$)
- Annualized changes in measured glomerular filtration rate as assessed by plasma clearance of iohexol ($mGFR_{iohexol}$) from baseline through month 18.

In the FACETS trial, the primary end point was the percentage of patients with a ≥ 50% reduction from baseline to month 6 in the average number of GL-3 inclusions per kidney interstitial capillary.

Measured glomerular filtration rate as assessed by plasma clearance of iohexol
A single intravenous dose of Omnipaque 300 (5 mL) was administered in a peripheral vein according to a standardized procedure. Blood samples were collected at 120, 150, 180, and 240 minutes post-injection. In general, one group was to be used for infusion, and the opposite group was to be used for sampling. Iohexol concentrations were determined using a validated assay. The data were used to calculate the $mGFR_{iohexol}$ value. This outcome ($mGFR_{iohexol}$) was a primary efficacy end point in the ATTRACT trial, and was a secondary efficacy end point in the FACETS trial.

Estimated glomerular filtration rate assessed by the CKD-EPI equation
The $eGFR_{CKD-EPI}$ was calculated using the following equation: $eGFR_{CKD-EPI} = 141 \times \min(\text{serum creatinine}/\kappa,1)^{alpha} \times \max(\text{serum creatinine}/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.1018$ (if female) x 1.159(if black) where κ is 0.7 for females and 0.9 for males, alpha is –0.329 for females and –0.411 for males, min indicates the minimum of SCR/κ or 1, and max indicates the maximum of serum creatinine/κ or 1. This outcome ($eGFR_{CKD-EPI}$) was a primary efficacy end point in the ATTRACT trial, and was a secondary efficacy end point in the FACETS trial.

Estimated glomerular filtration rate assessed by the Modification of Diet in Renal Disease equation
The estimated GFR assessed by the Modification of Diet in Renal Disease equation ($eGFR_{MDRD}$) was calculated by the central laboratory for every visit except visit 14 using the following equation: $eGFR_{MDRD} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 1.212$ (if patient's race is black or African-American) x 0.742 (if patient is female). This outcome ($eGFR_{MDRD}$) was a secondary efficacy end point in both the ATTRACT and the FACETS trials.

24-Hour urine collection
A 24-hour urine sample was collected at every study visit. These samples were used to measure 24-hour urine protein, albumin, and creatinine. The 24-hour urine protein and the 24-hour urine albumin: creatinine ratio were secondary efficacy end points in both the ATTRACT and the FACETS trials.

Cardiac echocardiogram
An echocardiogram was used to measure cardiac parameters including LVMI, left ventricular ejection fraction (LVEF), fractional shortening at diastole, and posterior wall thickness (LVPWT); and the intraventricular septal wall thickness (IVSWT). The LVMI, LVEF, LVPWT, and IVSWT were secondary outcomes in the ATTRACT trial, while only the

LVMI was measured in FACETS and it was not listed as a secondary or exploratory efficacy end point.

Lyso-Gb3

The plasma globotriaosylsphingosine (lyso-Gb3) biomarker is effective at diagnosing hemizygote and variant males and heterozygous females who are both symptomatic and asymptomatic. In terms of any correlation with clinical manifestations, it appears that high lyso-Gb3 exposure is an independent risk factor for white matter lesions in male FD patients and for left ventricular hypertrophy (LVH) in females. One observational study observed significant correlations observed between lyso-Gb3/creatinine and ERT status, different mutational types (suggesting predictive value in clinical severity), and age. However, it was determined that urine lyso-Gb3 is not a good predictor for kidney involvement as there was no correlation observed with eGFR.[22] No minimal clinically important difference (MCID) in either plasma or urine lyso-Gb3 has been identified. Both ATTRACT and FACETS trials assessed changes in the concentration of plasma lyso-Gb3 as an exploratory efficacy end point.

Renal, cardiac, or cerebrovascular events, or death

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

Renal events were defined, as follows:

- A decrease in $eGFR_{CKD\text{-}EPI} \geq 15$ 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.

Cardiac events were defined as myocardial infarction, unstable cardiac angina, new symptomatic arrhythmia (requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation), and congestive heart failure (New York Heart Association Class III or IV).

Cerebrovascular events were defined as stroke and transient ischemic attack.

The composite clinical outcome was a secondary efficacy end point in both the ATTRACT trial and it was not assessed in the FACETS trial.

Short-Form 36-Item Health Survey

The SF-36 (with version 2 being the most up-to-date version) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[23] The SF-36 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[23-25] Scores can be calculated for each of the eight domains. The SF-36 also provides two component summaries, the PCS and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status.[23,24] While there is a general acceptance of a 2.5- to 5-point range for the MID of the SF-36, there was no evidence identified to support this in patients with FD. No specific MCID or MCID range has been specifically determined for patients with FD (Appendix 5). The SF-36 was a secondary efficacy end point in both the ATTRACT and FACETS trials.

The Brief Pain Inventory

The Brief Pain Inventory (BPI) pain and interference instrument was primarily developed and used to assess how cancer pain interferes with or influences patients' lives.[26,27] It has subsequently been accepted and validated as a measure that can assess how pain affects or interferes with daily functioning in patients with many different diseases and in health care settings.[26,28,29] The BPI is a self-reported measure that assesses both pain and how pain affects/interferes with life.[27,29] It is composed of eight questions relating to pain, with four of these questions having a rating scale between 0 and 10, one diagrammatic picture question asking about the pain location, and three other questions pertaining to pain and pain relief.[29] For the assessment of pain, the following scores indicate pain severity; a score of 1 to 4 indicating "mild pain," a score of 5 to 6 indicating "moderate pain," and a score of 7 to 10 indicating "severe pain."[26,29] The ninth question is split into seven separate questions, which are grouped to assess three main areas of daily functioning: sleep, physical functioning, and emotional functioning. These Items are also scored between 0 and 10.[27,29] The references that summarized the BPI did not state how the overall score is created and what is its range. A benchmark for the BPI MCID has been suggested to be a change of 1 point (or 0.5 of its standard deviation) on the interference scale.[27,28] However, no MCID has been explicitly identified for patients with FD. The BPI was a secondary efficacy end point in both the ATTRACT and the FACETS trials.

The Gastrointestinal Symptoms Rating Scale

The Gastrointestinal Symptoms Rating Scale (GSRS) is a patient-reported outcome that was originally designed to ascertain changes in gastrointestinal (GI) symptoms in patients with irritable bowel syndrome (IBS) and peptic ulcer disease (PUD).[30] In its complete form, the GSRS rating scale examines the full range of GI symptoms by including impact on daily living, intensity of symptoms, duration of attacks, and frequency of attacks. However, individual variables can be removed from the scale to ascertain changes within specific indications that may not require the full list.[30] There are 15 individual variables that examine both upper and lower GI symptoms and they are scored between 0 and 3, with higher scores indicating more severe symptoms. These upper GI symptom variables include abdominal pain, heartburn, acid regurgitation, sucking sensation in the epigastrium, nausea and vomiting, borborygmus (abdominal rumbling), abdominal distention, eructation (belching), and increased flatus (passing gas). Scoring for these is determined by the following: 0 = none or transient, 1 = occasional, 2 = prolonged/frequent/troublesome, 3 = severe/continuous.[30] The lower GI symptom variables include decreased passage of stools (0 = once/day, 1 = every third day, 2 = every fifth day, 3 = every seventh day/less frequently), increased passage of stools (0 = once/day, 1 = three times/day, 2 = five times/day, 3 = seven or more times/day), loose stools, hard stools (0 = normal, 1 = somewhat, 2 = runny/hard, 3 = watery/hard fragmented), urgent need for defecation (0 = normal, 1 = occasional, 2 = frequent, 3 = inability to control), and feeling of incomplete evacuation (0 = feeling of complete, 1 = somewhat difficult, 2 = definitely difficult, 3 = extremely difficult).[30] The MCID for the GSRS has been estimated at 0.6 for abdominal pain, 0.8 for reflux, 0.4 for diarrhea, 0.7 for indigestion, and 0.7 for constipation subscales. However, this was determined in a cohort of renal transplant patients changing from mycophenolate mofetil to enteric-coated mycophenolate sodium.[31] No MCID was identified for patients with FD. The FACETS trial assessed GI symptoms using the GSRS and it was considered a secondary efficacy end point; the ATTRACT trial did not assess GI symptoms.

Kidney Biopsy Assessment for Interstitial Capillary GL-3 (primary efficacy end point in the FACETS trial)

Kidney biopsy samples were assessed for GL-3 by histological evaluation under light microscopy. The evaluation was conducted independently by three renal pathologists blinded to treatment group and visit date. GL-3 inclusions in interstitial capillaries were scored using a quantitative method to determine the average number of GL-3 inclusions per capillary. A decrease in the number of inclusions per capillary by at least 50% over six months is interpreted as likely to be associated with clinical benefit.[10] GL-3 inclusions per kidney interstitial capillary was the primary efficacy end point in the FACETS trial, and it was not assessed in the ATTRACT trial.

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product, biologic (at any dose), or medical device that did not necessarily have a causal relationship with the treatment.[10,19] An AE could be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medical product. An AE could include the onset of new illness and the exacerbation of pre-existing conditions. A serious AE (SAE) was any AE occurring at any dose that resulted in death, was life-threatening, resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, required inpatient hospitalization, or was a congenital anomaly or birth defect.

Statistical Analysis

In the ATTRACT trial, the co-primary efficacy outcome measures assessed renal function at 18 months. 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 ATTRACT study was not designed to demonstrate non-inferiority on the co-primary end points, but rather the comparability of the two treatments. Pre-specified criteria were developed in conjunction with the European Medicines Agency to define comparability of GFR results for migalastat and ERT. Migalastat would be considered to have comparable effectiveness to ERT if both of the following criteria were met:

- The difference between the means for the annualized change in GFR for 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%

The sample size for the 18-month randomized treatment period was calculated based on the co-primary end point and measure of comparability specified above. The planned enrolment was approximately 50 patients (approximately 30 patients in the migalastat group and 20 patients in the ERT group). The annual decline of $mGFR_{iohexol}$ in the ERT group was expected to be between 2 and 4 mL/min/1.73 m^2 with a standard deviation of approximately 7.5 to 8.5 mL/min/1.73 m^2. If the expected mean annual decline of $mGFR_{iohexol}$ in the migalastat group ranged from 3 to 7.5 mL/min/1.73 m^2, and the above assumptions were correct, the Clinical Study Report indicated that a sample size of 50 patients would allow for a substantial overlap of the 95% CIs for the mean change from baseline in $mGFR_{iohexol}$ for the two treatment groups.

Statistical analysis of the co-primary outcomes in the ATTRACT was conducted via analysis of covariance (ANCOVA) with the following factors and covariates: treatment group, age, sex, baseline GFR ($mGFR_{iohexol}$ or $eGFR_{CKD\text{-}EPI}$) and baseline 24-hour urine protein. Linear regression slopes were used to calculate the annualized changes in GFR. ANCOVA was

also used for analyzing the echocardiographic outcomes (for LVMI, LVEF, LVPWT, IVSWT). Formal statistical analysis was not reported for 24-hour urine protein, the 24-hour albumin: creatinine ratio, health-related quality of life (HRQoL) outcomes (SF-36 and BPI) or biochemical outcomes (plasma lyso-Gb3). No adjustments for multiplicity were performed. Efficacy analyses were performed using the modified intention-to-treat (mITT) population. Missing efficacy data were not imputed.

In FACETS, the primary analysis compared the percentage of patients in the two treatment groups with a > 50% reduction from baseline to month 6 in the number of GL-3 inclusions per kidney interstitial capillary using an exact Cochran–Mantel–Haenszel test stratified by sex. A *P* value < 0.05 (two-sided) was required to conclude a statistically significant treatment effect. The intention-to-treat (ITT) population was used for the analysis of the primary efficacy end point. To provide adequate power to test the primary outcome, the trial intended to randomize 30 patients in each treatment group (total of 60 patients). The power would change based on the success (i.e., the percentage of patients with a ≥ 50% reduction from baseline to month 6 in the average number of GL-3 inclusions per kidney interstitial capillary) in each treatment group, where the power would be > 90% if the success rate was 66.7% in the migalastat treatment group and 20% in the placebo group and the power would be 75% if the success rate were 73.3% in the migalastat treatment group and 36.7% in the placebo group. The difference between the group means was compared using the t-test for the mean per cent change in urine GL-3, and the mean change in 24-hour urine protein. Slopes for $eGFR_{CKD\text{-}EPI}$, and $mGFR_{iohexol}$ from baseline to month 6 between migalastat and placebo groups were analyzed using an ANCOVA model that included treatment as a factor with the baseline value as a covariate and the treatment by baseline interaction. Statistical comparisons of HRQoL outcomes (BPI, SF-36) between migalastat and placebo during stage 1 (baseline to month 6) used an ANCOVA model, which included treatment, baseline, and the treatment by baseline interaction. The primary efficacy end point was also summarized by presenting the frequency and the difference of the proportion with the corresponding 95% confidence interval within each sex. No adjustments for multiplicity were performed. Patients who were missing the baseline kidney biopsy were not included in the analysis. Patients who had the baseline kidney biopsy and no month 6 biopsy were counted as failures for the primary analysis.

Analysis Populations

In the ATTRACT trial, the analysis of efficacy outcomes was based on an mITT population that included all randomized patients with mutations amenable to migalastat in the good laboratory practice HEK assay that received at least one dose of study drug and had both the baseline and a post-baseline efficacy measure of $mGFR_{iohexol}$ and a post-baseline measure of $eGFR_{CKD\text{-}EPI}$. The ITT population included all randomized patients regardless of their participation in the study beyond randomization. Patients were classified according to randomized treatment group. The safety population included all patients in the ITT population who received at least one dose of study drug. Patients were classified according to the treatment received.

In the FACETS trial, primary analysis was performed using the ITT population that included all randomized patients. Each patient was analyzed according to their original randomized treatment group. The per-protocol (PP) population included all randomized patients who had received at least one dose of study medication and had both the baseline (visit 1) and month 6 (visit 4) kidney biopsy. Patients were analyzed according to the actual treatment received in the PP population. The safety population included all randomized patients who

received at least one dose of study medication. All safety analyses were performed using the safety population and analyzed patients according to the actual treatment received.

Patient Disposition

In the ATTRACT trial, a total of 68 patients were screened and 60 were randomized. Of the 24 patients randomized to remain on ERT therapy, three patients withdrew informed consent prior to receiving study medication and were excluded from all analyses. As a result, the 57 randomized patients who received at least one 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 treatment group and 19 in the ERT continuation group). Of the 60 randomized patients in the ATTRACT trial, six patients randomized to remain on ERT therapy withdrew informed consent (of which three withdrew prior to first scheduled dose of study drug) and two randomized to migalastat (one withdrew consent and one had depression) (Table 8).

In the FACETS trial, a total of 180 patients were screened, 67 patients were randomized, and 113 patients were excluded (100 patients did not meet inclusion criteria, and 13 patients did not provide informed consent). The 100 excluded patients were a mix of patients without the amenable mutation and those with inadequate urine GL-3, or a combination of both criteria. Of the 67 randomized patients 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). Of the 67 randomized patients in FACETS, two patients in the placebo group withdrew (two withdrew consent and one became pregnant) and no patient discontinued in the migalastat group by end of stage 1 (Table 9).

Table 8: Patient Disposition for the ATTRACT Trial

	ATTRACT	
	Migalastat	**ERT**
Screened, N	68	
Randomized, N	36	24[a]
Randomized and treated	36[b]	21[c]
Discontinued, N (%)	2 (5.6)	3 (14.3)
Consent withdrawn	1	3
Depression	1	0
Completed 18-month controlled phase, N (%)	34[b] (94.4)	18[c] (85.7)
Patients with amenable mutations completed 18 month controlled phase	32	16
ITT, N	36[d]	24[d]
mITT, N	34[e]	18[e]
PP, N	NR	NR
Safety, N	36[f]	21[f]

ITT = intention-to-treat; mITT = modified intention-to-treat; NR = not reported; PP = per-protocol.
[a] Consent withdrawn by three patients prior to first scheduled dose of study drug.
[b] Includes two patients with non-amenable mutations.
[c] Includes two patients with non-amenable mutations.
[d] All randomized patients.
[e] Randomized patients with amenable mutations receiving at least one dose of study medication and having a baseline and post-baseline efficacy measures of $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$.
[f] All randomized patients who received ≥1 dose of study drug.
Sources: Hughes et al.[6] and NICE Migalastat for treating Fabry disease evaluation report.

Table 9: Patient Disposition for the FACETS Trial

	FACETS	
	Migalastat	**Placebo**
Screened, N	180	
Randomized, N	34	33
Number of patients who completed month 6, N (%)	34 (100)	30 (91)
Discontinued, N (%)	0	2
Consent withdrawn	0	1
Pregnancy	0	1
Number of patients in the Stage 2 population	34	30
Number of patients who completed month 12 (stage 2 population)	31 (94)	29 (97)
Discontinued, N	3	1
Consent withdrawn	2	0
SAE	1	1
Patients with amenable mutations N (%)	28 (82)	22 (67)
ITT, N[a]	34 (100)	33 (100)
mITT, N[b]	30 (88)	30 (91)
PP, N[c]	30 (88)	30 (91)
Safety, N[d]	34 (100)	33 (100)

ITT = intention-to-treat; mITT = modified intention-to-treat; PP = per-protocol.
[a] The intention-to-treat population includes all randomized patients regardless of their participation in the study beyond randomization.
[b] The modified intention-to-treat population includes all randomized patients who received at least one dose of study drug and had both the baseline and month 6 kidney biopsies.
[c] The safety population includes all randomized patients who received at least one dose of study drug.
[d] The PP population includes all randomized patients who have received at least one dose of study drug, had both the baseline and month 6 kidney biopsies, and had no major protocol violations.
Sources: Germain et al.[10]; Clinical study reports[20]; and NICE Migalastat for treating Fabry disease evaluation report.[7]

Exposure to Study Treatments

In the ATTRACT trial, the median duration of study drug was 540 days for the migalastat group and 524 days for the ERT group. In the FACETS trial, at the end of stage 1 (six-month double-blind period), the mean exposure was 5.91 months for the migalastat group and 6.11 months for the placebo group, while the median exposure was 5.95 months for the migalastat group and 6.01 months for the placebo group.

Critical Appraisal

Internal Validity

In both trials, patients were randomized using appropriate methods and adequate allocation concealment. In the FACETS trial, matched placebo was used to maintain blinding. The ATTRACT trial appropriately stratified patients by gender and by proteinuria; the FACETS trial appropriately stratified patients by gender. The FACETS trial used a block randomization procedure but with no indication of the number or size of blocks or how these related to the stratification factors. It is unclear if block sizes were fixed, which potentially could make the allocation of participants predictable, and selection bias might have been introduced.

The ATTRACT trial was open-label. Hence, a number of outcomes would be prone to detection bias and performance bias as patients, investigators, and outcome assessors would have known the treatment allocation. A possible exception is for assessment of echocardiographic parameters, which were read centrally in a blinded fashion. However, the method of blinding was not described, and it is unclear if there is a risk of detection bias in the assessment of echocardiographic parameters.

For the ATTRACT trial, the manufacturer indicated that a standard non-inferiority analysis comparing migalastat and ERT on the co-primary end points' 95% CIs was not possible due to the rarity of the illness and the resulting small sample size. Therefore, pre-specified criteria were developed in conjunction with the Scientific Advice Working Party of the European Medicines Agency to define comparability of GFR results for migalastat and ERT. However, no justification for these criteria was provided. While the ATTRACT trial met the pre-specified criteria for comparability, this should not be confused with unequivocal demonstration of equivalence, non-inferiority or superiority.

In the ATTRACT trial, apart from AEs, missing data were not appropriately accounted for, as missing efficacy data were not imputed. In addition, no sensitivity analyses were undertaken to account for missing data.

Despite randomized group allocation, there were baseline imbalances in several prognostic baseline characteristics in both randomized controlled trials between the migalastat and comparator groups. In both trials, patients in the migalastat group had a shorter time since diagnosis than those in the comparator group. (In the ATTRACT trial the median time since diagnosis was double that of the ERT group [9.4 years] compared with the migalastat treatment group [4.5 years]; in the FACETS trial median time since diagnosis was five years in the placebo group and 4.1 years in the migalastat treatment group.) The mean total urine protein collected over 24 hours was less in the migalastat group than in the comparator group for both trials (mean of 93 mg less in ATTRACT, and 110 mg less in FACETS), while the median total urine was higher in the migalastat group than the ERT group in the ATTRACT trial. In the ATTRACT trial, the mean age was four years older in the migalastat group than the ERT group. In the FACETS trial, a lower proportion of patients received an ACEI, ARB or RI at baseline (18% versus 39%) in the migalastat group than the placebo group, a lower proportion of patients in the migalastat group than the placebo group had received prior ERT (15% versus 36%), the mean age was five years younger in the migalastat group than the placebo group, and the proportion of patients who had an amenable GLA mutation was 15% higher in the migalastat group than the placebo group. The clinical expert indicated that some of these imbalances might introduce bias. Most of the introduced bias was in favour of migalastat, where age is particularly relevant, and would tend to bias the results against the older group of patients. Consequently, the imbalances in mean age between the groups would bias the results against migalastat in the ATTRACT trial and would bias the results in favour of migalastat in the FACETS trial. The results would also likely be biased in favour of migalastat in the FACETS trial because the treatment groups had a lower total urine protein collected over 24 hours in the migalastat group than those in the placebo group. The results would also likely be biased in favour of migalastat in both trials because in both trials the migalastat treatment groups had a shorter duration since diagnosis than the comparator groups. A lower proportion of patients in the migalastat group than in the comparator group for both trials were receiving an ACEI, ARB or RI at baseline, which would bias the results against migalastat. It is not clear in which direction the total urine protein would bias the results in the ATTRACT trial

because the mean was lower in the migalastat group than the ERT group, while the median was higher in the migalastat group than the ERT group.

There were imbalances in the number of patients dropping out between treatment groups in both trials. In the ATTRACT trial, 6% (n = 2) of patients dropped out of the migalastat group versus 25% (n = 6) of patients in the ERT group. In the FACETS trial no patients dropped out of the migalastat group whereas 9% (n = 3) of patients dropped out of the placebo group. It is unclear if the number of dropouts and the imbalances in dropouts would have altered the prognosis of the study groups, and the risk of attrition bias is also unclear. The fact that 25% of the patients receiving ERT in the ATTRACT dropped out is of concern, given the already small sample size (24 patients), and that these individuals did not contribute to the primary efficacy end point analysis.

Although ITT analyses were undertaken based on all randomized patients in both trials, the ITT population included some patients who were found after randomization not to have amenable mutations (6% and 8% of patients in the migalastat and ERT groups of the ATTRACT trial, and 18% and 33% of patients in the migalastat and placebo groups of the FACETS trial). The ATTRACT trial used an mITT analysis set for all efficacy analyses, which excluded patients with non-amenable mutations as well as patients with other protocol violations. Consequently, the mITT analysis set was effectively a PP population, and the term “modified ITT” is therefore potentially misleading.

Although the inclusion criteria of the studies specify that patients should have had a confirmed GLA mutation responsive to migalastat in vitro, the classification of mutations as amenable or non-amenable changed after the patients were enrolled in the phase III RCTs. These changes were a result of the mutation assay being validated and updated. However, it is unclear why there are differences between the ATTRACT and the FACETS trials in the total percentage of patients who were found not to have amenable mutations, as well as why there are imbalances between the study groups within FACETS in the proportions of patients who were found not to have amenable mutations. The manufacturer clarified that the timing of the good laboratory practices validation of the assay allowed better identification of eligible patients for the ATTRACT trial than for the FACETS trial, which was further along in its enrolment than the ATTRACT trial at the time the updated assay became available.

The baseline SF-36 PCS and BPI scores in the ATTRACT trial indicate that patients in the migalastat treatment group had, on average, a higher level of functioning and less pain at study entry compared with the ERT group. These differences were greater than the general MID for the PCS. For the BPI scores it is unclear if the differences between the migalastat and ERT are considered clinically meaningful.

Sample size calculation was reported in the FACETS study protocol. However, the intended power was not clear, given that the power calculation ranged between 75% and at least 90%.

Results of the statistical analyses in the ATTRACT trial for most efficacy outcomes were reported as means or medians separately for the migalastat and ERT groups, with limited presentation of differences between the migalastat and ERT groups and effect sizes, which makes it difficult to compare the results between groups.

In the FACETS trial, in addition to the dropouts reported in the disposition table, other data may have been missing if, for example, not all patients provided HRQoL measurements.

The number of participants contributing to the HRQoL outcomes in the FACETS trial was not reported, and the extent of missing HRQoL data is unclear. In the ATTRACT trial, the analyzed sample size for HRQoL outcomes was smaller than the mITT analysis sample size due to missing data.

Due to the short duration of the FACETS trial, it is not possible to draw any firm conclusions about effects of migalastat on HRQoL. Also, the statistical significance interpretation for GSRS is limited, as no variance measures were given for the six-month outcomes and only crude *P* value thresholds were presented. The clinical expert indicated that, with the exception of pain, the time is too short to draw any firm conclusions on most outcomes from the double-blind phase of the FACETS trial.

The clinical expert indicated that the threshold used in the ATTRACT trial for stratification (low: < 100 mg/24 hours; high: ≥ 100 mg/24 hours) is not high enough, and a stratification at proteinuria ≥ 300 mg/24 hours is preferred, as this threshold is more indicative of severe disease and would cut off patients with low-grade proteinuria.

In the FACETS trial, only 23 kidney biopsy samples were included in this analysis. The manufacturer clarified that only patients who had received migalastat in both stages would qualify for a kidney biopsy and that of the 10 patients who did have a kidney biopsy, six patients had non-amenable mutations and four patients did not have both a baseline and month 6 kidney biopsy. However, this does not diminish the importance of the fact that 10 of 33 eligible patients did not have biopsy results in a study that was intended to look at biopsy as a primary outcome.

In both trials, the potential implications of conducting multiple statistical tests were not considered, and no adjustment was made for multiple testing despite secondary end point analyses that would increases risk of type-1 (false-positive) error.

The European Medicines Agency Assessment Report for migalastat indicated that the GL-3 inclusions in renal tissue cannot be used for the prediction of the clinical benefit of migalastat because, even though a qualitative correlation between GL-3 inclusions and clinical outcome can be assumed, a quantitative relation cannot be established.[8]

External Validity

In the FACETS and ATTRACT trials the proportion of male participants was 35% and 44%, respectively. These differences are important as clinical symptoms and signs of FD generally manifest earlier and are typically more severe in males than in females.

Both trials enrolled patients with less severe manifestations than those expected in clinical practice. For instance, none of the trials had patients with renal failure, while in clinical practice it is likely that there would be a higher proportion of patients with this complication. Also, the Canadian data at the five-year follow-up shows that patients newly started on ERT in Canada have more advanced disease manifestations (baseline eGFR was 79 and baseline LVMI was 123.2 in Cohort 1b of the CFDI) than the patients included in the ATTRACT and the FACETS trials.[9] The clinical expert indicated that the patient population included in both trials had “extremely early and mild disease,” which makes it difficult to generalize the results to patients with advanced disease who are switching therapies. This assertion is supported by the 2017 Canadian Fabry Disease Treatment Guidelines, which indicate that both ATTRACT and the FACETS trials did not include patients with high levels of proteinuria, which is a known risk factor for adverse cardiovascular and renal events in FD, and that both trials involved patients with very mild disease manifestations.[15]

The clinical expert indicated that the key efficacy outcomes in the trials should have been hard clinical outcomes and not surrogate outcomes. In addition, outcomes identified as important based on patient input were heat and cold intolerance, fatigue, GI and heart-related issues, and reduced quality of life. In the ATTRACT trial, hard clinical outcomes were assessed (composite clinical outcome was used, comprising the rates of pre-specified renal, cardiac, and cerebrovascular events, and the rate of mortality), over 18 months. However, the study was not powered to compare treatment groups for these clinical outcomes. In addition, the clinical expert indicated that the definition of renal events used was aggressive, where changes in calculated GFR measurements on a day-to-day basis in healthy patients can be higher than those defined as a renal event. As a result the percentage of patients experiencing renal events in the ATTRACT might be higher than we would expect to see, but should not affect the between-group comparisons. Finally, neither trial had sufficient follow-up to look for an effect on stroke. Neither trial assessed heat and cold intolerance or fatigue, and the ATTRACT trial did not assess GI issues.

In the FACETS trial, a total of 180 patients were screened, and 113 patients were excluded (100 [55.6%] patients did not meet inclusion criteria, and 13 patients did not provide informed consent) indicating strict inclusion and exclusion criteria, which would make the generalizability of results questionable.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See Appendix 4 for detailed efficacy data.

No data were available for the following key efficacy outcomes: composite outcome of death, cardiovascular events, cerebrovascular events, or renal events in the FACETS trial; incidence of hospitalization in both trials; and improvement in gastrointestinal symptoms in the ATTRACT trial. In addition, no subgroup data were available for the key efficacy outcomes identified in the protocol. The following outcomes that were identified in the review protocol as other efficacy outcomes were not measured: nerve fibre conduction, neuropathic pain, tolerance to cold and heat, and exercise tolerance. Subgroup results by gender were available for the LVMI end point in the ATTRACT trial, and results by gender and proteinuria (< 100 mg/24 hours and ≥ 100 mg/24 hours) were provided for $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$. No other subgroup results were available.

Key Efficacy Outcomes

Renal, Cardiac, or Cerebrovascular Events or Death

In the ATTRACT trial an analysis of a composite clinical outcome composed of renal, cardiac, and cerebrovascular events, or death, was conducted as a secondary outcome. During the 18-month treatment period, the percentage of patients who had a renal, cardiac, or cerebrovascular event or who died was 29% (10 of 34) of the patients switched from ERT to migalastat compared with 44% (8 of 18) of the patients who remained on ERT. Overall, renal events were the most common, followed by cardiac events, which were higher in the ERT treatment group than the migalastat treatment group. No deaths occurred. In the migalastat group, renal events included increased proteinuria in six patients and decreased GFR in two patients, cardiac events were chest pain in one patient, and the other was ventricular tachycardia/chest pain. In the ERT group, renal events included increased proteinuria in four patients and decreased GFR in three patients; cardiac events were cardiac failure in one patient, one was dyspnea, one arrhythmia; and the

cerebrovascular event was transient ischemic attack (Table 10). The *P* value for the between-groups statistical comparison was 0.36, indicating no statistical significance between the treatment groups.[6] The FACETS trial did not report event outcomes.

Table 10: Number (%) of Patients in the mITT Population Who Experienced Composite Clinical Outcomes in the ATTRACT Trial[a]

	ATTRACT	
Component,[b] n (%)	**Migalastat (n = 34)**	**ERT (n = 18)**
Renal	8 (24%)	6 (33%)
Cardiac	2 (6%)	3 (17%)
Cerebrovascular	0 (0%)	1 (6%)
Death	0 (0%)	0 (0%)
Any	10 (29%)	8 (44%)

ERT = Enzyme replacement therapy; mITT = modified intention-to-treat.

[a] Composite clinical outcomes was patients who experienced death or one of the following specific listed renal, cardiac, or cerebrovascular events. Renal events were defined as a decrease in $eGFR_{CKD\text{-}EPI} \geq 15$ mL/min/1.73 m^2, with the decreased eGFR < 90 mL/min/1.73 m^2 relative to baseline and an increase in 24-hour urine protein ≥ 33%, with the increased protein ≥ 300 mg relative to baseline. Cardiac events were defined as myocardial infarction, unstable cardiac angina, new symptomatic arrhythmia (requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation), and congestive heart failure (New York Heart Association Class III or IV). Cerebrovascular events were defined as stroke and transient ischemic attack.

[b] In the migalastat group, renal events included increased proteinuria in six patients and decreased GFR in two patients. For cardiac events, one was chest pain and the other was ventricular tachycardia/chest pain. In ERT group, renal events included increased proteinuria in four patients and decreased GFR in three patients; cardiac events included one cardiac failure, one dyspnea, and one arrhythmia; the cerebrovascular event was transient ischemic attack.

Source: Hughes et al.[6]

Health-Related Quality of Life

The SF-36 v2 was used to collect HRQoL data. In the ATTRACT trial, changes from baseline did not exceed the minimum important difference at any time point for either the migalastat or the ERT group (Table 11). No between-group comparison was reported. In the FACETS trial, no statistically significant differences between placebo and migalastat groups were observed from baseline to month 6.[10]

Table 11: Patient-Reported Outcomes SF-36 and BPI-SF in the ATTRACT and FACETS Trials

	ATTRACT[a]		FACETS	
	Migalastat	ERT	Migalastat	
SF-36v2				
Physical component				
Baseline, n	34	16	NR	NR
Baseline, mean ± SEM	47.8 ± 1.9	40.4 ± 2.7	NR	NR
Change from baseline to month 18, n	31	16	NR	NR
Change from baseline to month 18, mean (95% CI)	0.96 (−1.0 to 2.9)	−1.92 (−6.7 to 2.8)	NR	NR
Mental component				
Baseline, n	34	16	NR	NR
Baseline, mean ± SEM	49.3 ± 1.8	50.6 ± 2.6	NR	NR
Change from baseline to month 18, n	31	17	NR	NR
Change from baseline to month 18, mean (95% CI)	0.08 (−3.3 to 3.4)	−0.41 (−4.3 to 3.5)	NR	NR

CI = confidence interval; ERT = enzyme replacement therapy; NR = not reported; SEM = standard error of the mean; SF-36v2 = Short Form Health Survey with 36 questions, version 2 (higher score represent less disability; range for each component: 0-100).
[a] Based on all randomized patients with amenable mutations.
Source: Hughes et al.[6]

Patient-Reported Symptoms

The Brief Pain Inventory

Questions based on BPI-Pain Severity Component were used to collect pain outcome. In the ATTRACT trial changes from baseline did not exceed the MCID at any time point for either the migalastat or the ERT group (Table 12). No between-group treatments comparison was reported. In the FACETS trial, no statistically significant differences between placebo and migalastat groups were observed from baseline to month 6 for the changes in BPI severity component.[10]

Table 12: Changes in BPI-SF in The ATTRACT and The FACETS Trials

	ATTRACT[a]		FACETS	
	Migalastat	ERT	Migalastat	
BPI-SF (Pain Severity)				
Baseline, n	34	17	NR	NR
Baseline score, mean ± SEM	1.29 ± 0.31	2.12 ± 0.56	NR	NR
Change from baseline to month 18, n	34	17	NR	NR
Change from baseline to month 18, mean (95% CI)	0.15 (−0.56 to 0.88)	−0.19 (−0.98 to 0.59)	NR	NR

BPI-SF = Brief Pain Inventory Short Form pain severity component; CI = confidence interval; ERT = enzyme replacement therapy; NR = not reported; SEM = standard error of the mean.

[a] BPI-SF= Brief Pain Inventory Short Form pain severity component (higher scores represent more pain; range: 1-10).

Source: Hughes et al.[6]

Gastrointestinal Symptoms Rating Scale

The GSRS was only measured in the FACETS trial. At six months, a greater percentage of patients receiving migalastat had an improvement in the diarrhea domain compared with placebo (38% versus 9%), and there was a statistically significant difference in scores for this domain between the two groups (−0.3 for migalastat versus 0.2 for placebo, $P < 0.05$) (Table 13).

Table 13: Changes in Gastrointestinal Symptoms Rating Scale in the FACETS Trial (ITT Population With Amenable Mutations)[a]

GSRS Domain	Diarrhea		Reflux		Indigestion		Constipation		Abdominal Pain	
Treatment Group	Migalastat	Placebo	Migalastat	Placebo	Migalastat	Placebo	Migalastat	Placebo	Migalastat	Placebo
Mean Baseline Values (n)										
All Patients	2.3 (28)	2.1 (22)	1.4 (28)	1.4 (22)	2.5 (28)	2.4 (22)	1.9 (28)	2.0 (22)	2.1 (28)	2.3 (22)
Change from Baseline to Month 6 (Double-Blind Period)										
All Patients	−0.3[b]	0.2	−0.1	0.2	−0.1	−0.1	0.1	0.2	0	0
Change from Baseline (Migalastat) or Month 6 (Placebo) to Month 24 (OLE Migalastat Treatment)										
All Patients	−0.5 (−0.9 to −0.1)[d]		−0.2 (−0.5 to 0.2)		−0.4 (−0.7 to −0.04)[d]		−0.4 (−0.7 to 0.0)[e]		−0.2 (−0.5 to 0.1)	

OLE = open-label extension.
[a] Least-squares means for change from baseline.
[b] $P = 0.03$ using analysis of covariance.
[c] $P = 0.047$ using analysis of covariance.
[d] Statistically significant.
[e] Trend based on 95% CIs with the upper bound of 0.
Sources: Hughes et al.[6] and Germain et al.[10]

Other Efficacy Outcomes

Renal Function

ATTRACT Trial

In the ATTRACT trial, the co-primary end points $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ demonstrated that migalastat and ERT had comparable effects on renal function over 18 months. Using the mITT population, mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ was –0.40 mL/min/1.73 m^2 (95% CI, –2.272 to 1.478; n = 34) in the migalastat group compared with −1.03 mL/min/1.73 m^2 (95% CI, −3.636 to 1.575; n = 18) in the ERT group. Mean annualized rate of change in $mGFR_{iohexol}$ was −4.35 mL/min/1.73 m^2 (95% CI: −7.65 to −1.06; n = 34) in the migalastat group compared with −3.24 mL/min/1.73 m^2 (95% CI: −7.81 to 1.33; n = 18) in the ERT group (Table 16). The pre-specified criteria for comparability of migalastat and ERT were met for the outcomes of both co-primary end points $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$: the annualized means were within 2.2 mL/min/1.73 m^2/year and the 95% CIs for the means had greater than 50% overlap. Therefore, patients who switched from ERT to migalastat met the pre-specified criteria for comparability to patients who remained on ERT.

Results of the annualized change from baseline to month 18 for the ITT and PP population are presented in Table 17. Within-group results seem to be in the same direction as the

mITT population (except for the PP population in the ERT group for the $eGFR_{CKD-EPI}$ end point, which indicated there was an increase in $eGFR_{CKD-EPI}$). However, the manufacturer did not provide the difference in mean annualized change between treatment groups, and it is not possible to comment on whether the ITT and PP population met the pre-specified comparability criteria or not (Table 17).

The manufacturer provided the annualized change from baseline to month 18 for the mITT population by gender and proteinuria (< 100 mg/24 hours and ≥ 100 mg/24 hours) using two different measures of eGFR ($eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$) (Table 18, Table 19, Table 20, and Table 21). The manufacturer did not provide the difference in mean annualized change between treatment groups, and it is therefore not possible to comment on whether or not these met the pre-specified criteria (Table 18, Table 19, Table 20, and Table 21).

In the ATTRACT trial, at baseline, in the mITT population, the mean 24-hour urine protein was 259.6 ± 422.22 mg/day in the migalastat group and 417.4 ± 735.5 mg/day in the ERT group, in which higher protein in the urine may signify kidney damage or disease. The mean change from baseline to month 18 was 49.2 ± 199.5 mg/day for the migalastat group and 194.5 ± 690.8 mg/day for the ERT group (Table 27). No formal between-groups statistical comparison was undertaken for this outcome.

In the ATTRACT trial, at baseline, the 24-hour urine albumin: creatinine ratio in the migalastat group was 13.55 ± 28.91 mg/mmol and in the ERT 21.89 ± 47.08 mg/mmol in the mITT population. Change from baseline to month 18 for migalastat was 5.78 ± 19.66 mg/mmol and 14.34 ± 40.20 mg/mmol for ERT (Table 27). No formal between-groups statistical comparison was undertaken for this outcome.

FACETS Trial

Changes in renal function were evaluated as secondary end points in the FACETS trial. The six-month change in mean (± SEM) mGFR in the ITT analysis in FACETS was −1.19 ± 3.4 mL/min/1.73 m^2 in the migalastat group (n = 34) and 0.41 ± 2.0 mL/min/1.73 m^2 in the placebo group (n = 33).[7] The FACETS trial also reported two different measures of eGFR ($eGFR_{CKD-EPI}$, and $eGFR_{MDRD}$), but these showed inconsistent changes in direction from baseline (Table 22). No formal between-groups statistical comparison was undertaken for this outcome.

In the FACETS trial, in patients with amenable mutations, the mean 24-hour urine protein at baseline was 268.7 ± 344 mg/day in the migalastat group and 655.3 ± 760 mg/day in the placebo group. The mean change from baseline to month 6 was: 2.2 ± 252 mg/day for the migalastat group and −12.9 ± 224 mg/day for the placebo group (Table 28). No formal between-groups statistical comparison was undertaken for this outcome.

Interstitial Capillary GL-3

In the FACETS trial, the primary end point at the end of the double-blind period (six months) was the kidney interstitial capillary GL-3 responder analysis (defined as ≥ 50% reduction from baseline in the average number of GL-3 inclusions per interstitial capillary). A decrease in the number of inclusions per capillary by at least 50% over six months is interpreted as likely to be associated with clinical benefit.[10] In the ITT population (i.e., patients with amenable and non-amenable mutations based on the migalastat amenability assay), a response was seen in 41% of patients receiving migalastat and 28% of patients receiving placebo (P = 0.3). Based on the responder analysis, the primary end point was not met because the difference between groups was not statistically significant. The

difference in median per cent change in interstitial capillary GL-3 inclusions between migalastat and placebo was also not statistically significant. The mean difference in the change in the percentage of interstitial capillary with no GL-3 inclusions was statistically significantly greater with migalastat compared with placebo (7.3% versus 1.3%, respectively; *P* = 0.042) (Table 23).

A post hoc analysis at the end of the double-blind period (six months) was conducted in the patients with amenable mutations. The change from baseline analysis demonstrated that six months of treatment with migalastat was associated with a statistically significantly larger reduction in the average number of GL-3 inclusions per interstitial capillary compared with placebo: –0.250 ± 0.103 versus +0.071 ± 0.126, respectively; *P* = 0.008. There was no difference between migalastat and placebo in patients with non-amenable mutations (Table 23).

Cardiac Function

In the ATTRACT trial, the mean baseline LVMI was 95.3 ± 22.7 g/m^2 in the migalastat group and 92.9 ± 25.7 g/m^2 in the ERT group (mITT). A decrease in LVMI indicates that a treatment might be beneficial in people with cardiac complications, and LVMI decreased significantly from baseline to 18 months in patients who switched from ERT to migalastat (−6.6 g/m^2; 95% CI, −11.0 to −2.2); in patients who continued on ERT, the value at 18 months showed no statistically significant change from baseline (−2 g/m^2; 95% CI, −11.0 to 7.0). Subgroup analysis showed that LVMI decreased from baseline to month 18 in both males and females in the migalastat group (mean change: 13 males [−9.4 g/m^2; 95% CI, −17.036 to −1.795] and 18 females [−4.5 g/m^2; 95% CI, −10.301 to 1.244]). In the ERT group LVMI decreased from baseline to month 18 in females (n = 7) as well (–7.2 g/m^2; 95% CI, −15.889 to 1.463); in males (n = 6) LVMI increased from baseline to month 18 (4.05 g/m^2; 95% CI, −15.362 to 23.462) (Table 24). No formal between-groups statistical comparison was undertaken for this outcome.

The mean baseline LVEF was 64.0 g/m^2 in the migalastat group and 61.1 g/m^2 in the ERT group (mITT). The mean change from baseline to month 18 was –1.1 g/m^2 in the migalastat group and –0.49 g/m^2 in the ERT group. The left ventricular posterior wall thickness in diastole decreased from baseline to month 18 in the migalastat group (mean change, –0.035 cm) but not in the ERT group (mean change, 0.029 cm) in the mITT Population (Table 24). No formal between-groups statistical comparison was undertaken for this outcome.

In the FACETs trial, no changes from baseline in LVMI were seen during the initial six-month, double-blind, placebo-controlled period (Table 25).[7] No formal between-groups statistical comparison was undertaken for this outcome.

Other Biochemical Markers

In the ATTRACT trial, the mean baseline values of plasma lyso-Gb3 for migalastat was 9.1 ± 10.8 nmol/L and 17.6 ± 20.7 nmol/L for ERT. Plasma lyso-Gb3 levels remained low and stable for up to 18 months in patients with amenable mutations who switched from ERT to migalastat, and in patients remaining on ERT (Table 26). No formal between-groups statistical comparison was undertaken for this outcome.

In the FACETS trial, in patients with amenable mutations, Plasma lyso-Gb3 at baseline was 47.3 ± 62.2 nmol/L in the migalastat treatment group and 41.8 ± 39.1 nmol/L in placebo treatment group. After six months of treatment, the lyso-Gb3 concentration in the migalastat

group was 36.1 ± 45.9 nmol/L, and in the placebo group it was 42.2 ± 43.1 nmol/L (Table 26). No formal between-groups statistical comparison was undertaken for this outcome.

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol).

Adverse Events

In the ATTRACT trial, the percentage of patients with a treatment-emergent AEs (TEAEs) was similar for the migalastat (94%) and ERT (95%) groups. The most frequent (≥ 25%) TEAEs reported in the migalastat group were nasopharyngitis (33%) and headache (25%), which were also the most frequent TEAEs reported in the ERT group (33% nasopharyngitis and 24% headache) (Table 14).

In the FACETS trial, the number of patients who experienced at least one TEAE during the double-blind period (six months) was similar between treatment groups (91% in the migalastat group and 91% in the placebo group). The most frequently reported TEAEs in the migalastat group during the double-blind period (six months) were headache (35%), nasopharyngitis (18%), nausea (12%), fatigue (12%), paresthesia (12%), and pyrexia (12%). The most frequently reported TEAEs in the placebo group were headache (21%), pain in extremity (12%), fatigue (12%), and paresthesia (12%) (Table 14).

Serious Adverse Events

In the ATTRACT trial, the percentage of patients with a SAE was less common in the migalastat group (19%) than in the ERT group (33%). The most commonly occurring SAE was chronic heart failure deterioration, which occurred four times in one patient while receiving ERT. Chest pain was reported for three patients (once each) receiving migalastat. Morbid obesity was reported for two patients receiving migalastat (Table 14).

In the FACETS trial, the frequency of SAEs was lower in the migalastat group (6%), compared with the placebo group (12%). Only two patients in the migalastat group experienced SAEs during the double-blind period (six months); each patient experienced one SAE (post-procedural hematoma and hydronephrosis), both of which were assessed as unrelated to study drug. Both patients had amenable mutations (Table 14).

Withdrawals Due to Adverse Events

In the ATTRACT trial, during the 18-month randomized treatment period, no patient discontinued treatment due to a TEAE (Table 14).

In the FACETS trial, no patient discontinued due to a TEAE in the migalastat group during the double-blind period (six months); one patient (3%) discontinued due to a TEAE in the placebo group during double-blind period (six months) (Table 14).

Mortality

There were no deaths in either study (Table 14).

Table 14: Harms

	ATTRACT		FACETS	
AEs	**Migalastat N = 36**	**ERT N = 21**	**Migalastat N = 34**	**Placebo N = 33**
Patients with > 0 AEs, N (%)	34 (94)	20 (95)	31 (91)	30 (91)
Most common AEs[a]				
Nasopharyngitis	12 (33)	7 (33)	6 (18)	2 (6)
Headache	9 (25)	5 (24)	12 (35)	7 (21)
Dizziness	6 (17)	2 (10)		
Influenza	5 (14)	4 (19)		
Abdominal pain	5 (14)	2 (10)		
Diarrhea	5 (14)	2 (10)		
Nausea	5 (14)	2 (10)	4 (12)	2 (6)
Back pain	4 (11)	3 (14)		
Upper respiratory tract infection	4 (11)	1 (5)		
Urinary tract infection	4 (11)	1 (5)		
Cough	3 (8)	5 (24)		
Vomiting	3 (8)	3 (14)		
Sinusitis	3 (8)	3 (14)		
Arthralgia	3 (8)	2 (10)		
Bronchitis	2 (6)	3 (14)		
Edema peripheral	2 (6)	2 (10)		
Vertigo	1(3)	2 (10)		
Dry mouth	1(3)	2 (10)		
Gastritis	1(3)	2 (10)		
Pain In extremity	1(3)	2 (10)	0	4 (12)
Dyspnea	1(3)	2 (10)		
Procedural pain	0	2 (10)		
Fatigue			4 (12)	4 (12)
Paresthesia			4 (12)	4 (12)
Pyrexia			4 (12)	1 (3)
SAEs				
Patients with > 0 SAEs, N (%)	19%	33%	2 (6)	4 (12)
Most common SAEs				
Bacterial infection			0	1 (3)
Meningitis viral			0	1 (3)
Post-procedural hematoma			1 (3)	0
Post-procedural hemorrhage			0	1 (3)
Anaplastic large cell lymphoma T- and null-cell types			0	1 (3)
Hydronephrosis			1 (3)	0
WDAEs, N (%)	0	0	0	1 (3)
Number of deaths, N (%)	0	0	0	0

AE = adverse events; ERT = enzyme replacement therapy; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Frequency > 10%.
Sources: Clinical study report[20] and EMA report.[8]

Discussion

Summary of Available Evidence

Two trials, ATTRACT and FACETS, met the inclusion criteria for this review. Both trials were phase III, multi-centre RCTs. The ATTRACT RCT was open-label and compared migalastat against ERT over an 18-month period in patients with FD who were receiving ERT prior to study entry and who had migalastat-responsive GLA mutations. Patients were randomized to either continue receiving ERT or to switch from ERT to migalastat. Co-primary outcomes were changes in renal function assessed by measured and estimated GFR ($mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$). The FACETS RCT was double-blind and compared migalastat with placebo over a six-month period in patients with FD and with amenable mutations who had not previously received ERT within six months of eligibility screening. The primary outcome was a biochemical measure: changes in inclusions of GL-3 in interstitial capillary cells.

Key limitations in both trials were the small sample size, no adjustment for multiple statistical testing, baseline imbalances in patient characteristics between the trial groups in both RCTs (of particular concern in trials with small participant numbers), and unbalanced attrition, which reflects uncertainty around the key outcomes. In addition, in the ATTRACT trial, there was limited presentation of differences between the migalastat and ERT groups and no formal consideration of effect sizes, no justification was provided for the pre-specified criteria that defined comparability of GFR results for migalastat and ERT, and the relevance of the value as an acceptable difference in the measured or estimated GFR (2.2 mL/min/1.73 m^2) over a period of 18 months is questionable. The FACETS trial had a short duration in the double-blind period and the clinical expert indicated that, with the exception of pain, the time is too short to draw any firm conclusions on most outcomes from the double-blind phase of the FACETS trial.

Interpretation of Results

Efficacy

The clinical expert indicated that the key efficacy outcomes in the trials should have been hard clinical outcomes and not surrogate outcomes. In the ATTRACT trial, hard clinical outcomes were assessed (composite clinical outcome was used, comprising the rates of pre-specified renal, cardiac and cerebrovascular events, and the rate of mortality) over 18 months. During the 18-month treatment period, the proportion of patients who had a renal, cardiac, or cerebrovascular event, or who died was 29% (10 of 34) of the patients who switched from ERT to migalastat compared with 44% (8 or 18) of the patients who remained on ERT. The *P* value for the between-groups statistical comparison was 0.36, indicating no statistical significance between the treatment groups.[6] Overall, renal events were the most common (24% with migalastat versus 33% with continued ERT), followed by cardiac events (6% with migalastat versus 17% with continued ERT). No deaths occurred. The study was not powered to compare treatment groups for these clinical outcomes. In addition, the clinical expert indicated that the definition of renal events used was aggressive, where changes in calculated GFR measurements on a day-to-day basis in healthy patients can be higher than those defined as a renal event. However, the aggressive definition of renal events was applied equally to the ERT and migalastat groups.

Neither trial had sufficient follow-up to look for an effect on stroke, so it is not clear if migalastat would be useful to reduce the risk of stroke in FD.

From the patient group input received by CDR on this submission, it is clear that patients consider improved quality of life, reduction in pain, and reduction in gastrointestinal problems to be important outcomes of treatment. Both ATTRACT and FACETS assessed HRQoL using the SF-36 and pain using the BPI short form. In addition, FACETS employed the GSRS. In the ATTRACT trial, at baseline, the SF-36 PCS and BPI scores indicated that patients in the migalastat treatment group had, on average, a higher level of functioning and less pain at study entry compared with the ERT group. These differences were greater than the general MCID for the PCS, but it is unclear if the differences in the BPI scores are strong enough to have an influence on the interpretation of the effect estimates. The BPI pain severity component indicated that patients experienced only mild pain at baseline in the ATTRACT trial. Over the 18-month study period, mean scores for the SF-36 MCS and PCS, and the BPI increased marginally in the migalastat group over 18 months and decreased slightly in the ERT group. However, the differences were small, and the confidence intervals in all cases included zero. Also none of the changes from baseline exceeded the MID of 2 points in the SF-36 PCS, 3 points in the SF-36 MCS and the MCID of 1 point or 0.5 of its standard deviation for the BPI. No formal between-groups statistical comparison was undertaken for the SF-36 MCS, SF-36 PCS, or the BPI. Changes in the SF-36 after 18/24 months of migalastat therapy in patients with amenable mutations were reported in the FACETS trial. Significant improvements were seen in the vitality (mean increase: 4.0) and general health (mean increase: 4.5) domains of the SF-36 from baseline. However, a claim of statistical significance cannot be made because there was no adjustment for multiple statistical testing; the values for the other health domains of the SF-36 appeared to remain stable over the 18/24 month period. No statistically significant differences between placebo and migalastat groups were observed from baseline to month 6 for the SF-36 and changes in BPI severity component scores. Changes in GSRS scores indicated a greater improvement in diarrhea and reflux symptoms in the migalastat group compared with the placebo group, but no difference between the groups for indigestion, constipation, or abdominal pain were reported. Chan et al. estimated that the MCIDs were 0.6 for abdominal pain, 0.8 for reflux, 0.4 for diarrhea, 0.7 for indigestion, and 0.7 for constipation domains in the GSRS.[31] However, these MCIDs were not calculated for the FD patient population. The difference between treatment groups for the change from baseline to month 6 was not reported; and it was not possible to judge if the difference exceeded the MCID. After 18 or 24 months of migalastat treatment, patients in the FACETS trial exhibited statistically significant improvements in diarrhea and indigestion domains compared with baseline, and only diarrhea exceeded the MCID of 0.4 in all patients and in patients with symptoms at baseline. However, all results of HRQoL measures in the FACETS trial should be interpreted with caution because sample sizes were not reported and, due to the short duration of the double-blind period of the trial, it is not possible to draw any firm conclusions about effects of migalastat on HRQoL. In addition, the results from the FACETS trial on BPI indicated that migalastat does not have a beneficial effect on pain in comparison with placebo.

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.[1,32,33] In FD, slowing the progressive decline in renal function is a treatment objective. The pre-specified criteria for comparability of migalastat and ERT in the ATTRACT trial (a difference between the means for the annualized change in GFR for migalastat and ERT of no greater than 2.2 mL/min/1.73 m^2/year and 95% CIs for the means greater than 50% overlap) were met for

both the co-primary $mGFR_{iohexol}$ and $eGFR_{CKD-EPI}$ outcomes in the mITT population. However, these outcomes were associated with wide confidence intervals, indicating uncertainty. The manufacturer did not provide the difference in mean annualized change between treatment groups or state whether the 95% CIs for the means had greater than 50% overlap for the ITT and PP population, and it is not possible to comment on whether the ITT and PP populations meet the pre-specified criteria or not. It is typically recommended that non-inferiority trials assess outcomes based on both the ITT and PP populations, and the trial be considered positive if both ITT and PP analyses support non-inferiority.[34] While the ATTRACT trial was not a non-inferiority trial, but rather a comparability trial, there would have been better confidence in the results if the outcomes were assessed with the same rigour as is recommended for non-inferiority trials, in which analysis is conducted appropriately for the ITT and PP population and same results shown as the primary analysis. While the ATTRACT trial met the pre-specified criteria for comparability, this should not be confused with unequivocal demonstration of equivalence, non-inferiority, or superiority.[7] A retrospective chart review that assessed progression of nephropathy before ERT indicated that patients with higher baseline proteinuria levels were associated with more rapid declines in eGFR.[35] The rates of eGFR decline for male patients with baseline proteinuria < 100 mg/24 hours, 100-1,000 mg/24 hours, and ≥ 1,000 mg/24 hours were −1.6, −3.3 and −6.9 mL/min/1.73 m^2/year, respectively. The rates of eGFR decline for female patients with baseline proteinuria < 100 mg/24 hours, 100-1,000 mg/24 hours and ≥ 1,000 mg/24 hours were −0.66, −2.2 and −4.6 mL/min/1.73 m^2/year, respectively.[35] Given that approximately 42% of patients had proteinuria < 100 mg/24 hours in the ATTRACT trial, it is possible that patients might have had a minimal decline in eGFR even without treatment, and there is more uncertainty around the clinical effectiveness of migalastat compared with ERT. In ATTRACT trial, the 24-hour urine protein and albumin: creatinine ratio both increased but to a smaller extent in the migalastat group than the ERT group. The changes are uncertain.

The clinical expert indicated that in patients with well-preserved renal function (as in the ATTRACT trial), the CKD-EPI can overestimate renal function. In all patients, measured values such as iohexol would be considered more optimal than calculated values. While iohexol is considered the “gold standard for measuring GFR,” the results can be affected by the use of concomitant medications and by whether or not a patient is fasting. The use of concomitant medications was stable over the course of the study, but it was not stated in the ATTRACT trial if all measurements were done during the fasting state. For example, if the iohexol measurement was done while fasting but the serum creatinine value used for the CKD-EPI calculation was not undertaken during a fasting state, this could influence the differences between the measurements, particularly in patients with well-preserved renal function. Thus, if the values for CKD-EPI and iohexol are in the same direction but the absolute values for change differ, this could be a methodological issue. Results were provided by the manufacturer for the annualized change from baseline to month 18 for the mITT population by gender and proteinuria (< 100 mg/24 hours and ≥ 100 mg/24 hours) for the ATTRACT trial using two different measures of eGFR ($eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$). The values for $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ were not in the same direction for all subgroups, and sometimes differed by more than 3 mL/min and as the measures of renal function are not consistently concordant, then the value that is a more reliable measure should be used; this would be the measured value, which is iohexol. The trend for $mGFR_{iohexol}$ was that the ERT group is favoured in most of the analyses. Results from $mGFR_{iohexol}$ measures indicated that the ERT group is favoured in most of the analyses.

Changes in renal function were evaluated as secondary end points in the FACETS trial. The six-month change in mean (± SEM) mGFR in the ITT analysis in FACETS was −1.19 ± 3.4 mL/min/1.73 m^2 in the migalastat group (n = 34) and 0.41 ± 2.0 mL/min/1.73 m^2 in the placebo group (n = 33).[7] These results indicate that patients may have had better stabilization of GFR in the placebo group than the migalastat group. However, six months is likely too short a time to draw any conclusions about changes in renal function, especially given the relatively small sample sizes and large standard errors. The FACETS trial also reported two different measures of eGFR ($eGFR_{CKD-EPI}$, and $eGFR_{MDRD}$), but these showed inconsistent changes from baseline. No formal between-groups statistical comparison was undertaken for the measures of GFR. In the FACETS trial, the 24-hour urine protein increased in the migalastat group but decreased in the placebo group.

The primary 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 GL-3 inclusions, analyzed in the ITT population. This was higher in the migalastat group (40.6%; n = 34) than the placebo group (28.1%; n = 33), but the difference between groups was not statistically significant. As a result, the FACETS study did not meet its primary end point in the ITT population.

Cardiac complications are the main cause of death in patients with FD.[36,37] The ATTRACT trial only reported cardiac outcomes for the mITT analyses, and these indicated that migalastat did not influence LVEF but did improve left ventricular mass during the 18-month trial period. LVMI decreased statistically significantly from baseline to 18 months in patients in the migalastat group (−6.6 g/m^2; 95% CI, −11.0 to −2.2); while in patients who continued on ERT, the value at 18 months did not change from baseline (−2 g/m^2; 95% CI, −11.0 to 7.0). However, there is some uncertainty in these results as the number of patients included in this analysis (33 in the migalastat group and 16 in the ERT group) was lower than the number specified in the mITT population (34 patients in the migalastat group and 18 patients in the ERT group) with no reason given for the missing data. In addition, the study was underpowered, and it is impossible to conclude that migalastat is superior to ERT. Also, because the patients in the ATTRACT study had relatively mild degrees of LVH (baseline LVMI 95.3 g/cm^2) ATTRACT does not provide data on what effect the drug might have in later stages of the cardiac disease (when fibrosis is more prominent). No formal between-groups statistical comparison were undertaken for these outcome.

In the FACETS trial, no changes in LVMI were seen in the six-month double-blind period, which is expected due to the short duration. For patients 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.

In the ATTRACT trial, changes in plasma lyso-Gb3 were measured in the subgroups of patients with and without amenable mutations. In patients with amenable mutations, migalastat had the same effect as ERT in maintaining low levels of lyso-Gb3, while in patients without amenable mutations lyso-Gb3 increased in the migalastat group but not the ERT group. In the FACETS trial, plasma lyso-Gb3 concentrations declined in the migalastat group but not the placebo group, and this difference between groups after six months was statistically significant.

For the purposes of treatment with the chaperone therapy migalastat, GLA mutations are generally classified into types of mutations that are either “responsive” or amenable” and those that are “non-responsive” or “non-amenable” to treatment with migalastat.[17,18] While determining whether the mutations from males are amenable to migalastat is more precise

(as they have only one copy of the affected gene on their single X chromosome), females pose a different problem in that their cells contain a mixture of mutant and wild-type forms of alpha-Gal A, both of which are responsive to migalastat.[17] See Appendix 7 for more details about the GLA mutational assay. It is important to note that even if a patient is identified as having an amenable mutation, an individual's response to treatment with migalastat can vary considerably.[5] The Health Canada–approved product monograph indicates that "the genotype of alpha-Gal A determines the nature and extent of the clinical response to migalastat in patients with FD. For amenable genotypes, the extent of the migalastat-induced accumulation of the alpha-Gal A protein can vary significantly. Therefore, response to migalastat can differ according to the specific amenable mutation. For non-amenable genotypes, migalastat may result in a net loss of alpha-Gal A activity, potentially worsening the disease condition."[5] The Health Canada–approved product monograph also states that "In clinical trials, individual response to migalastat treatment varied considerably among patients with amenable mutations and that patients should be assessed for treatment response or failure when initiating migalastat, and monitored periodically thereafter (every six months or more frequently) throughout the treatment, and that the predictability of the extent of clinical outcome in amenable patients is limited."[5]

In the OLE of either the ATTRACT and FACETS trials there were no apparent differences in the efficacy outcomes $eGFR_{CKD\text{-}EPI}$, $eGFR_{MDRD}$, and $mGFR_{iohexol}$, 24-hour urine protein, composite clinical outcomes, echocardiographic outcomes, HRQoL, and patient-reported symptoms when compared with the main studies. While there were no apparent differences in efficacy, conclusions regarding the long-term efficacy of migalastat in patients with FD are limited due to the absence of a comparator group and the short duration of treatment.

Harms

No deaths occurred in either of the trials or the OLE studies. In the ATTRACT trial, during the 18-month randomized treatment period, no patient discontinued treatment due to a TEAE. In the FACETS trial, no patient discontinued due to a TEAE in the migalastat group during the double-blind period (six months), one patient (3%) discontinued due to a TEAE in the placebo group during the double-blind period (six months). SAEs in ATTRACT were less frequent in the migalastat group than the ERT group (19% versus 33%). The most commonly occurring SAE was chronic heart failure deterioration, which occurred four times in one patient while receiving ERT. Chest pain occurred once in each of three patients receiving migalastat. Morbid obesity was reported in two patients receiving migalastat. In the ATTRACT OLE, 16 patients (31%) in the migalastat-migalastat group and three (20%) patients in the ERT-migalastat group experienced serious adverse events. In the FACETS trial, the frequency of SAEs was lower in the migalastat group (6%), compared with the placebo group (12%). Only two patients in the migalastat group experienced SAEs during the double-blind period (six months); each patient experienced one SAE (post-procedural hematoma and hydronephrosis), both of which were assessed as unrelated to the study drug. In the OLE of the FACETS trial, SAEs were experienced by five (17%) and six (21%) of patients in the migalastat-migalastat and placebo-migalastat group, respectively. Migalastat was not associated with the infusion-associated reactions that commonly occur with ERT. Also, there was no risk of infections associated with vascular access because migalastat is an oral agent. Input from patient groups often described infusion treatment for ERT as cumbersome and problematic, as infusion centres (often far away from patients) and the times associated with the actual infusions significantly affect their lives.

In the ATTRACT trial, the majority of patients in both the migalastat and ERT groups (94% to 95% of patients) experienced a TEAE. The most frequent adverse events were nasopharyngitis and headache, and these did not differ in frequency between the migalastat and ERT groups. In the FACETS trial, the majority of patients (91%) in both the migalastat and placebo groups experienced a TEAE. The most frequent TEAE was headache and nasopharyngitis, and these were both more frequent in the migalastat group (35% and 18% respectively) than in the placebo group (21% and 6%). No new safety signals were identified in the OLE of either the ATTRACT and FACETS trial. A potential limitation of the adverse event data is that the trials were of relatively short duration and included a small number of patients, where the median duration of study drug administration in the migalastat-migalastat groups was 30 months in the ATTRACT trial (n = 30) and 23.7 months in the FACETS trial (n = 27).

Potential Place in Therapy[b]

Prior to migalastat, ERT was the only pharmacological treatment option for FD patients. ERT is a major advance in the treatment of patients with FD in that it can stabilize renal function and progressive increases in left ventricular size in many patients with this disorder. There are still many challenges in treating FD patients. ERT requires regular biweekly intravenous infusions. While the manufacturers of ERT support patients to receive these infusions in their home, this is not available in all parts of the country and infusions remain an inconvenient and minimally invasive form of therapy. While most patients receive their infusions through a peripheral intravenous line, some patients lose peripheral intravenous access over time and will require insertion of a central venous catheter (CVC) with its attendant risks. An effective and well-tolerated oral medication such as migalastat would therefore provide treatment that was more convenient for patients who tolerate ERT and would remove the need to insert a CVC in the small number of adult patients who require one.

Severe allergic reactions to ERT for FD are uncommon but there are a small number of patients with severe allergic reactions who either have to stop ERT or have to take pre-medications such as hydrocortisone, which have their own adverse effects. While an effective oral alternative would be very useful in patients who cannot tolerate ERT, it is unlikely that migalastat can fill that role in that the more severe infusion reactions often occur in patients with the more severe mutations (e.g., null mutations) and these mutations are not usually amenable to chaperone therapy. Thus, an effective treatment alternative for patients who cannot tolerate ERT is likely to remain an unmet need, even with the availability of migalastat. Due to the psychological impact of regular venepuncture in children with FD, it is more common to insert a CVC for ERT infusions, making effective oral therapy even more of an advantage in children than in adults, but as migalastat is not indicated for children under the age of 18 this also will remain an unmet need. Furthermore, as migalastat is not indicated in patients with a GFR < 30 mL/min/1.73m^2, some patients with amenable mutations may not be able to use this oral option and will need to remain on ERT.

While ERT is beneficial in some of the manifestations of FD (e.g., renal, cardiac, GI), it is not helpful with other manifestations, including some (e.g., pain, stroke) that come with major impacts on patient quality of life. Also, some patients with ERT-responsive disease

[b] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

manifestations may continue to progress despite ERT. Hypotheses to explain such progression may include:

- Timing. If ERT is introduced at later stages of the disease, fibrosis (which is not ERT-responsive) rather than substrate accumulation (which is ERT-responsive) is the dominant pathological feature.
- Antibodies. Most males with FD will make antibodies to the ERT products. Unfortunately, as there is no international standardization of antibody assays, it is difficult to tease out what the effect of these antibodies might be on treatment response, although high-titre antibodies are associated with some adverse changes on surrogate biomarker profiles.
- Distribution. ERT does not cross into the brain and this may be related to its lack of efficacy on stroke, although the mechanisms of stroke in FD are not known.

There are likely other unknown factors that can influence response to ERT treatment. It is not clear how migalastat might affect these unmet needs. In terms of the disease manifestations treatable with ERT, it is encouraging that left ventricular mass declined in the patients who were switched from ERT to migalastat. The authors hypothesize that this might be related to improved tissue penetration of the small molecule, but as the study was underpowered it is not possible to conclude that migalastat is superior to ERT. Also, the patients in the switch study had relatively mild degrees of LVH (baseline LVMI 96.5 g/cm^2) and ATTRACT does not provide data on what effect the drug might have in later stages of the cardiac disease (when fibrosis is more prominent). Data from the FACETS and ATTRACT trials suggest that migalastat does not have a beneficial effect on pain, although specific trials designed to answer this question have not been performed. Neither trial has had sufficient follow-up to look for an effect on stroke, and it is unclear if migalastat would be useful in reducing the risk of stroke in FD.

ERT for FD is currently prescribed for patients who have established manifestations of the disease (i.e., in the secondary prevention setting) and is not currently recommended for patients who do not have evidence of disease involvement. Since 2006, all Canadian patients are followed through the CFDI, which provides funding for ERT (supported by the provinces) while collecting registry data to provide feedback to the payers on the outcomes of the Canadian patients. The ERT treatment guidelines undergo evidenced-based review on an annual basis and are available online (www.garrod.ca). The most recent version of the guidelines (2017) does include guidance on migalastat and the indications for use and monitoring of migalastat therapy are similar to those for ERT. All Canadian patients have to be approved by a panel of five physicians before they are eligible for publicly funded treatment. Patients who do not meet the treatment guidelines are not approved for publicly funded therapy, although they would be eligible to receive it if they had private drug insurance. It is expected that migalastat, if available, would also be run through this same approval mechanism, at least as long as the CFDI continues to act on behalf of the provinces. (Currently the CFDI contract has been extended to September 2019.) If treatment approvals for migalastat are run through the CFDI, it would not be expected that the availability of the oral product would alter the number of patients who are eligible for treatment. A small number of patients (three in the first five years of the CFDI registry as reported by Sirrs et al.) who are eligible for ERT decline this therapy. It is possible that some patients who decline ERT may accept an oral therapy if they have an amenable mutation. As a result, the availability of an oral therapy may increase slightly the total number of patients who receive therapy in Canada. If the intention of the provinces is not to centralize migalastat prescriptions through the CFDI, then some other means to control

prescribing should be in place; the availability of an oral drug increases the number of physicians who might feel confident prescribing therapy, given that the logistical issues around setting up ERT infusions are intimidating to physicians with limited experience. In Canada, immediately prior to instituting centralized control of ERT prescriptions through the CFDI, several patients who did not meet treatment criteria were started on ERT by non-expert physicians who were pressured to do so by the patients and the manufacturers. Without control over prescribing and with the availability of a well-tolerated oral agent, non-expert physicians may be pressured into considering treatment for patients who do not meet treatment guidelines, even though there are no data supporting the use of any type of treatment (ERT or oral) in the primary prevention setting.

The 2017 version of the CFDI guidelines made recommendations about the place in therapy for Canadian patients and these are available online at www.garrod.ca. Several issues are discussed in those guidelines for those with amenable mutations:

- The available data on migalastat as a first-line therapy (FACETS) involve patients with relatively mild disease manifestations (baseline eGFR 94, baseline LVMI 93-101). If patients met Canadian treatment guidelines at this mild level of disease, it could be considered as a possible first-line therapy.
- The available data on switching from ERT to migalastat (ATTRACT) is also in patients with very mild disease (baseline MDRD eGFR 85, LVMI 95). In patients with disease stabilized at this level on ERT, a switch could be considered.
- For patients with more significant disease manifestations, the data on the effects of migalastat are lacking. It is possible that some clinicians might prefer to treat such patients with ERT for an interval of several years first (when the effects on disease parameters can be better predicted) before considering a switch, and until more experience is available with migalastat in more advanced patients. The comfort level of physicians with using migalastat in this setting is likely to vary across the country.
    - The Canadian data at five years show that patients newly started on ERT in Canada9 are more advanced (baseline eGFR 79 and LVMI 123) than the patients in the ATTRACT study.
- It is possible that migalastat might be the preferred initial treatment option in younger patients (even if they have more advanced disease then the FACETS cohort), but to avoid the deleterious psychological effects of biweekly intravenous enzyme infusions on a child, migalastat is not indicated for patients below the age of 18 at the current time.
- It is possible that some patients whose physicians feel they are appropriate candidates to switch to migalastat may be reluctant to do so as there is a high prevalence of anxiety and depression in the Fabry cohort and some patients may be anxious about changing therapy. This may change over time as more patients in the country become familiar with the drug.

Monitoring of migalastat-treated patients is likely to be similar to that recommended for ERT. The manufacturer maintains a database of amenable mutations and evaluation of the mutation is required for all patients as part of the diagnostic process. If there was a novel mutation for which the utility of chaperone therapy was not known, then testing in the HEK cell line would be required. Presumably, this would be at the expense of the manufacturer. It is notable that the testing used to identify amenable mutations has evolved over time. As an example, the clinical trial of treatment-naive patients[10] included 17 patients who were originally thought to have amenable mutations and then were found not to be amenable with changes to the assay. This technology may continue to evolve over time (although no such changes to the assay are currently planned by the manufacturer) and it cannot be predicted how this might affect the number of patients potentially eligible for the oral

therapy. If reclassification of amenability status of mutations occurs over time, then it might not be apparent for two to four years that the drug is ineffective as some manifestations (such as cardiac enlargement, which is a dominant feature of FD) are very slow to evolve. Increased monitoring of patients who have demonstrated long-term stability on ERT may be advisable after a switch to migalastat.

Conclusions

Two trials (ATTRACT and FACETS) met the inclusion criteria for this review. Both trials were phase III, multi-centre RCTs that enrolled patients with FD who had migalastat-responsive GLA mutations. While the ATTRACT trial met the pre-specified criteria for demonstrating comparability of migalastat and ERT for the co-primary end points $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$, there is some uncertainty around the clinical effectiveness of migalastat compared with ERT because of the wide confidence intervals for the key efficacy outcomes, as well as concerns related to the internal validity of the trial, including imbalances in the study group demographic characteristics and unbalanced attrition. The ATTRACT trial was a comparability trial, which should not be confused with, or considered as, an equivalence, non-inferiority, or superiority trial. The FACETS study did not meet its primary end point (changes in inclusions of GL-3 in interstitial capillary cells) in the ITT population. In both trials the effect of migalastat on clinically meaningful outcomes was uncertain, mainly because any observed effects on clinically meaningful outcomes (e.g., HRQoL, hard outcomes, and patient-reported symptoms) were marginal and limited by methodological considerations, including no between-group statistical testing and no detailed reporting of results. The safety profile of migalastat was similar to ERT and placebo in the controlled phase of the trials. While there were no apparent differences in safety results for migalastat between the controlled phases of the studies and the OLE, conclusions regarding the long-term safety of migalastat in patients with FD are limited due to the absence of a comparator group and the short duration of treatment.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

One joint patient input submission was provided by the Canadian Fabry Association (CFA) and the Canadian Organization for Rare Disorders (CORD) whereby CORD performed the background research, conducted the interviews, prepared the survey, analyzed the data, and prepared the submission in collaboration with the CFA.

The CFA is an association that aims to improve the quality of life for any person affected by Fabry disease (FD) through the support of research, public education, advocacy, and awareness. In the past two years, Sanofi Genzyme, Shire, Amicus (the manufacturer of the drug under review), and Protalix have provided monetary funds to the CFA.

CORD is a registered charity that both provides a voice for patients with rare disorders and advocates for health policy and a health care system that works for these patients. In the past two years, Sanofi Genzyme, Shire, and Amicus have provided monetary funds to CORD.

Neither CFA nor CORD declared any conflict of interests with regard to the preparation of this submission.

2. Condition-Related Information

Patient perspectives were obtained from written individual testimonials, semi-structured interviews, and an Internet survey developed by CORD in collaboration with the CFA. The interviews and testimonials were used to seek patient experiences and perspectives, which were subsequently used to both develop the survey and provide context for data interpretation and validation. The survey (provided in both official languages) was distributed through the CFA database and posted on the CFA website, with a request to be further distributed to other patients with FD and their relatives. In addition, the survey was sent to the Fabry Australia organization, the National Fabry Disease Foundation (US), as well as to one patient in Belgium and two patients in Norway, (all currently being treated with migalastat). It consisted of open-ended questions, rating scales, and forced-choice options and was active between May 23 and June 15, 2017. In total, this submission was based on two testimonials and four interviews (all completed in patients with FD), and 84 survey responses (of which 74% had FD and qualified for enzyme replacement therapy [ERT], 11% had FD and did not qualify for ERT, 11% were caregivers, and 4% were patient advocates or clinicians). The majority of respondents were from Canada (90%), 58% were female, 39% were male (with some choosing not to self-identify), and the median age of respondents was 53 years (with a range between 20 and 99 years of age).

FD significantly affects the physical and emotional well-being of the patient along with severely affecting their ability to perform daily activities. Severe, sharp, or excruciating pain and swelling, particularly in the hands and feet, is often proclaimed to be the most bothersome symptom. Patients are also often intolerant to heat and cold. Symptoms such as fatigue and lack of energy significantly affect patients' ability to perform daily activities. In addition, gastrointestinal problems, cognitive impairment (such as lack of concentration, poor memory, and difficulty learning), cardiovascular problems, stroke, transient ischemic attacks, excessive sweating, ringing in ears, skin lesions or rash, and nervous system

issues (such as numbness and tingling) are also commonly experienced. All of these symptoms have a severe impact on school performance, the ability to undertake certain jobs or to perform up to certain expectations, the ability to partake in social activities, and the ability to perform the normal tasks of living. As one patient stated, *"It has limited employment through battling fatigue, swelling, cognitive functions, and sensitivity to heat/cold…. Not being able to be on my feet, limited choices of work… Emotionally devastating as nothing to take away pain."* Depression and mood swings are often experienced by patients, in part due to the symptomatology of the disease and also in its subsequent restrictions on the lives of patients. In addition to social and employment challenges, patients also experience financial issues, which can subsequently add to the depression and emotional challenges.

Since this is genetic disease, patients are also confronted with the impacts of the disease on the family, often across generations. Patients have often had to watch the devastating effects of loved ones go through the disease; one patient described the following: *"My brother went into kidney failure in mid 20's, fractured both hips during grand mal seizure… kidney transplant lasted 10 + years, then had a stroke, had kidney failure again, had heart failure and open heart surgery to replace damaged valves... had stroke during heart surgery - did not survive... He died at 46."* There is a significant amount of guilt and emotional stress associated with the possibility of actually passing FD on to children. As one patient stated, *"I had to watch my two sons grow up suffering the hands and feet pain, three day bouts of pain and fever, not being able to participate in any school sports (it would trigger pain), hardly any social life at all, etc. I did not experience the same physical symptoms as my sons, but I lived with the pain and guilt feelings of watching them grow up suffering themselves."* Some patients have decided to forgo having children due to the possibility that they may pass on the gene. This can also have a negative emotional and psychological effect.

3. Current Therapy-Related Information

Most patient respondents had taken or were still on ERT. Patients noted an improvement in their symptoms on ERT, including organ protection, increased energy, ability to work (or return to work), socialize, and carry out daily activities, and a reduction in pain in their extremities. Some patients even felt that they had reversed some of their previous cardiovascular issues. Patients also noted that ERT also helped them against an early death, as evidenced by the fact that some were still living on ERT past the ages of relatives that had succumbed at an earlier age. However, a significant number of patients also noted that they continued to experience symptoms related to their FD; some still experiencing moderate or severe symptoms and some symptoms were experienced frequently. All this being said, most were still happy that some, if not all, of their difficult symptoms were somewhat, if not totally, resolved.

The infusion treatment for ERT was often described as cumbersome and problematic because infusion centres (often far away from patients) and the times associated with the actual infusions significantly affect their lives. As one patient stated, *"I often miss work to get to appointments regarding my Fabry disease, as most are 3 hours away from me. As a family, we must plan every other weekend around my treatment time."* In addition, ERT treatment is not cheap; therefore, many patients and their families have financial concerns.

Also on the minds of patients is the fact that ERT may not be working for them because of the specific mutation they harbour. As one patient noted, *"There are 14 living members of my family with Fabry disease…. My mother has many heart issues and lives in pain every day. My brother has had strokes, heart problems, gastro issues and lives with severe pain every day. I have similar problems, TIAs, heart issues, pain and gastro. My son (16) is always in pain and gastro issues. There is some proof that ERT does not work for our mutation."* Therefore, having a new treatment alternative is something that patients and their families welcome.

4. Expectations About the Drug Being Reviewed

While patients ultimately want a cure for FD that is risk-free and permanent, they realize that this currently is not the case. Therefore, their hope is for new therapies that will be as effective as possible in slowing the disease progression, reducing symptoms, and avoiding organ damage, and one that has few to no side effects. Patients are hopeful that the oral formulation of migalastat will circumvent their need to attend infusion sessions, which are time-consuming and often force families to plan their activities and lives around attending them. There is the hope that there will be no special requirements for storage and handling, which will allow them to travel more freely for work or pleasure. They also believe that there will be better compliance with the oral formulation and that costs will be reduced. In addition, patients are hopeful for a more effective treatment, as they perceive it will allow the enzyme to "remain longer in the body at a stable level," either through more frequent dosing or a slow-release therapy.

Eight patients who responded had experience with migalastat through a clinical trial, extended clinical trial, or compassionate access (some patients said they did not know the difference among these pathways). Times on migalastat varied between a few months to more than two years, with all reporting that they were still on migalastat. Patients noted positive benefits on migalastat in comparison with ERT, particularly with the administration and management of the drug as well as better symptom management and potentially long-term organ protection. Some patients spoke of increased energy and increased mental functioning (better concentration). Side effects that were experienced by patients were few to none; the only two mentioned included a slight numbing feeling of the stomach and vaginitis (which was not enough for either patient to stop taking the medication).

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Epub Ahead of Print **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 13, 2017
Alerts:	Biweekly search updates until November 15, 2017 (date of CDEC meeting)
Study Types:	No filters were applied to limit the retrieval by study type.
Limits:	No date or language limits were used Conference abstracts were excluded Animal studies excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number (CAS, UNII)
.nm	Name of substance word
.tn	Drug trade name (Embase)
ppez	Ovid database code; MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches
1	(migalastat* or Galafold* or Amigal* or GR181413A or GR-181413A or hgt 3310 or hgt3310 or AT1001 or AT-1001 or NB-DGJ or C4XNY919FW or CLY7M0XD20 or 108147-54-2 or 75172-81-5).ti,ab,kf,ot,hw,rn,nm.
2	1 use ppez
3	migalastat/
4	(migalastat* or Galafold* or Amigal* or GR181413A or GR-181413A or hgt 3310 or hgt3310 or AT1001 or AT-1001 or NB-DGJ or C4XNY919FW or CLY7M0XD20 or 108147-54-2 or 75172-81-5).ti,ab,kw.
5	(Galafold or Amigal).tn.
6	or/3-5
7	6 use oemezd
8	2 or 7
9	8 not conference abstract.pt.
10	exp animals/
11	exp animal experimentation/ or exp animal experiment/
12	exp models animal/
13	nonhuman/
14	exp vertebrate/ or exp vertebrates/
15	or/10-14
16	exp humans/
17	exp human experimentation/ or exp human experiment/
18	or/16-17
19	15 not 18
20	9 not 19
21	remove duplicates from 20

OTHER DATABASES

PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH and keywords used as per MEDLINE search, with appropriate syntax used.	
Trial registries (clinicaltrials.gov and others)	Same keywords used as per MEDLINE search.	

Grey Literature

Dates for Search:	July 2017
Keywords:	Galafold, migalastat, Amigal Fabry disease, Fabry's disease
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Giugliani R, Waldek S, Germain DP, Nicholls K, Bichet DG, Simosky JK, et al. A Phase 2 study of migalastat hydrochloride in females with Fabry disease: selection of population, safety and pharmacodynamic effects. Mol Genet Metab. 2013 May;109(1):86-92.	Phase II non-pivotal trial
Germain DP, Giugliani R, Hughes DA, Mehta A, Nicholls K, Barisoni L, et al. Safety and pharmacodynamic effects of a pharmacological chaperone on alpha-galactosidase A activity and globotriaosylceramide clearance in Fabry disease: report from two phase 2 clinical studies. Orphanet J Rare Dis. 2012 Nov 24;7:91. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527132	Phase II non-pivotal trial
Benjamin ER, la Valle MC, Wu X, Katz E, Pruthi F, Bond S, et al. The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat. Genet Med. 2017 Apr;19(4):430-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5392595/pdf/gim2016122a.pdf	Non-randomized study
Oder D, Nordbeck P, Wanner C. Long Term Treatment with Enzyme Replacement Therapy in Patients with Fabry Disease. Nephron. 2016];134(1):30-6. Available from: https://www.karger.com/Article/Pdf/448968	Review
Mehta A. Fabry disease: A review of current enzyme replacement strategies. Expert Opinion on Orphan Drugs. 2015;3(11):1319-30.	Review

Appendix 4: Detailed Outcome Data

Table 15: Summary of Baseline Characteristics by Gender for the ATTRACT Trial (Safety Population)

	ATTRACT			
	Migalastat		ERT	
	Male	Female	Male	Female
N	16	20	9	12
Age (years)				
Mean (SD)	47.9 (15.35)	52.5 (12.38)	43.6 (12.50)	51.0 (16.71)
Median (min, max)	51.5 (19, 67)	54.0 (18, 70)	44.0 (18, 57)	50.5 (22, 72)
Years since diagnosis, mean (SD)	9.1 (11.61)	11.1 (12.11)	10.3 (11.79)	15.8 (12.95)
$mGFR_{iohexol}$ (mL/min/1.73 m^2)				
Mean	81.99	82.67	85.47	82.17
SD	20.031	16.936	17.066	28.722
Median	81.30	80.70	85.10	79.50
Min, max	51.7, 124.0	57.0, 111	66.4, 112.6	33.0, 132.2
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)				
Mean ± SEM	89.75	89.449	97.461	94.525
SD	25.928	19.4149	16.750	21.5017
Median	85.086	86.853	95.681	100.416
Min, max	51.33, 145.12	62.04, 123.94	71.21, 129.52	44.83, 127.89
$eGFR_{MDRD}$ mL/min/1.73 m^2, mean (SD)	82.7 (23.32)	84.2 (21.02)	89.9 (17.74)	86.2 (20.31)
Left ventricular mass index (g/m^2), mean (SD)	103.119 (27.6869)	90.210 (17.8507)	109.781 (21.5515)	76.019 (17.2081)
ERT, n (%)				
Agalsidase beta	5 (31)	6 (30)	3 (33)	5 (42)
Agalsidase alfa	10 (62)	14 (70)	6 (67)	7 (58)
Use of ACEI/ARB/RI, n (%)	7 (44)	9 (45)	6 (67)	5 (42)
Amenable GLA mutation, n (%)	14 (88)	20 (100)	8 (89)	11 (92)
Proteinuria > 100 mg/24 hours, n (%)	NA	NA	NA	NA
Proteinuria > 150 mg/24 hours, n (%)	NA	NA	NA	NA
Proteinuria > 300 mg/24 hours, n (%)	NA	NA	NA	NA
Proteinuria > 1,000 mg/24 hours, n (%)	NA	NA	NA	NA
Urine albumin:creatinine ratio (mg/mmol), n	15	20	9	11
Mean (SD)	17.7259 (40.442)	10.153 (13.587)	34.2013 (63.09826)	6.1123 (9.03936)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; $eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; RI = renin inhibitor; SD = standard deviation; SEM = standard error of mean.

Source: Amicus Therapeutics.[21]

Table 16: Annualized GFR From Baseline to Month 18 in the ATTRACT Trial (mITT Population)

	ATTRACT			
	Migalastat, mean ± SEM[a] (95% CI) n = 34	ERT, mean ± SEM[a] (95% CI) n = 18	Means within 2.2 mL/min/1.73 m^2/year	> 50% overlap of the 95% CI
ANCOVA				
$eGFR_{CKD-EPI}$	−0.40 ± 0.93 (−2.27 to 1.48)	−1.03 ± 1.29 (−3.64 to 1.58)	Yes	Yes
$mGFR_{iohexol}$	−4.35 ± 1.64 (−7.65 to −1.06)	−3.24 ± 2.27 (−7.81 to 1.33)	Yes	Yes
$eGFR_{MDRD}$	−1.51 ± 0.95 (−3.43 to 0.40)	−1.53 ± 1.32 (−4.20 to 1.13)	NA	NA

ANCOVA = analysis of covariance with the following factors and covariates (treatment group, sex, age, baseline GFR ($mGFR_{iohexol}$ or $eGFR_{CKD-EPI}$) and baseline 24-hour urine protein; CI = confidence interval; $eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; mITT = modified intention-to-treat population; NA = not assessed; SEM = standard error of mean.

[a] Least-squares means.

Source: Hughes et al.[6]

Table 17: Annualized GFR From Baseline to Month 18 in the ATTRACT Trial (ITT and PP Populations)

	ATTRACT			
	Migalastat, mean ± SEM[a] (95% CI),	ERT, mean ± SEM[a] (95% CI),	Means within 2.2 mL/min/1.73 m^2/year	> 50% overlap of the 95% CI
ITT population				
$eGFR_{CKD–EPI}$	–0.229 ± 1.1224 (–2.482 to 2.024)	–2.849 ± 1.4647 (–5.790 to 0.091)	NA	NA
$mGFR_{iohexol}$	–4.286 ± 1.5218 (–7.341 to –1.231)	–2.895 ± 1.9821 (–6.875 to 1.084)	NA	NA
$eGFR_{MDRD}$	NA	NA	NA	NA
PP population				
$eGFR_{CKD–EPI}$	–0.226 ± 0.9047 (–2.058 to 1.605)	0.265 ± 1.5199 (–2.812 to 3.342)	NA	NA
$mGFR_{iohexol}$	–3.447 ± 1.5497 (–6.584 to –0.310)	–2.604 ± 2.5946 (–7.857 to 2.648)	NA	NA
$eGFR_{MDRD}$	NA	NA	NA	NA

CI = confidence interval; $eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; ITT = intention-to-treat; NA = not assessed; PP = per-protocol; SEM = standard error of mean.

[a] Least-squares means.

Source: Amicus Therapeutics.[21]

Table 18: Annualized GFR From Baseline to Month 18 in the ATTRACT Trial (mITT Population – Male)

	ATTRACT			
	Migalastat, mean (SD)	ERT, mean (SD)	Means within 2.2 mL/min/1.73 m^2/year	> 50% overlap of the 95% CI
$eGFR_{CKD-EPI}$	–1.461 (3.2259)	–0.836 (7.6999)	NA	NA
$mGFR_{iohexol}$	–3.288 (8.7207)	–5.465 (5.7973)	NA	NA
$eGFR_{MDRD}$	NA	NA	NA	NA

CI = confidence interval; $eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; mITT = modified intention-to-treat; NA = not assessed; SD = standard deviation.

Source: Amicus Therapeutics.[21]

Table 19: Annualized GFR From Baseline to Month 18 in the ATTRACT Trial (mITT Population – Female)

	ATTRACT			
	Migalastat, mean (SD)	ERT, mean (SD)	Means within 2.2 mL/min/1.73 m^2/year	> 50% overlap of the 95% CI
$eGFR_{CKD-EPI}$	–0.044 (4.9117)	–2.019 (7.5730)	NA	NA
$mGFR_{iohexol}$	–5.301 (10.0143)	0.530 (10.5750)	NA	NA
$eGFR_{MDRD}$	NA	NA	NA	NA

CI = confidence internval; $eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; mITT = modified intention-to-treat; NA = not assessed; SD = standard deviation.

Source: Amicus Therapeutics.[21]

Table 20: Annualized GFR From Baseline to Month 18 in the ATTRACT Trial (mITT Population – Proteinuria ≥ 100 mg/24 hours)

	ATTRACT			
	Migalastat, mean (SD)	ERT, mean (SD)	Means within 2.2 mL/min/1.73 m^2/year	> 50% overlap of the 95% CI
ANCOVA (note: the files do not specify the use of ANCOVA as the statistical approach)				
$eGFR_{CKD-EPI}$	–2.252 (2.8249)	–2.696 (8.2978)	NA	NA
$mGFR_{iohexol}$	–2.843 (8.6361)	–1.227 (10.9909)	NA	NA
$eGFR_{MDRD}$	NA	NA	NA	NA

CI = confidence internval; ANCOVA = analysis of covariance; $eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; mITT = modified intention-to-treat; NA = not assessed; SD = standard deviation.

Source: Amicus Therapeutics.[21]

Table 21: Annualized GFR From Baseline to Month 18 in the ATTRACT Trial (mITT Population – Proteinuria < 100 mg/24 hours)

	ATTRACT			
	Migalastat, mean ± SEM[a] (95% CI)	ERT, mean ± SEM[a] (95% CI)	Means within 2.2 mL/min/1.73 m^2/year	> 50% overlap of the 95% CI
ANCOVA (note: the files do not specify the use of ANCOVA as the statistical approach)				
$eGFR_{CKD-EPI}$	1.431 (SD 5.0204)	0.912 (SD 5.0579)	NA	NA
$mGFR_{iohexol}$	–6.535 (SD 10.2495)	–3.950 (SD 3.9494)	NA	NA
$eGFR_{MDRD}$	NA	NA	NA	NA

CI = confidence internval; ANCOVA = analysis of covariance; $eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; $mGFR_{iohexol}$ = measured GFR using iohexol clearance; mITT = modified intention-to-treat; NA = not assessed; SD = standard deviation.

Source: Amicus Therapeutics.[21]

Table 22: Mean Change in GFR From Baseline to Month 6 in the FACETS Trial (ITT Population Excluding Patients With Non-Amenable Mutations)

	FACETS	
	Migalastat-Migalastat	Placebo-Migalastat
$eGFR_{CKD-EPI}$		
Baseline		
n	28	22
Mean (SD)	94.4 (26.98)	90.6 (17.13)
Stage 1 (during the double-blind period), Month 6		
n	28	20
Mean (SD)	95.3 (28.48)	91.4 (20.78)
Change from baseline, Mean (SD)	0.9 (8.34)	1.2 (7.91)
$eGFR_{MDRD}$		
Baseline		
n	28	22
Mean (SD)	87.1 (30.25)	83.0 (18.78)
Stage 1 (during the double-blind period), Month 6		
n	28	20
Mean (SD)	90.2 (32.59)	83.7 (20.82)
Change from baseline, Mean (SD)	3.1 (14.35)	1.1 (8.60)

$eGFR_{CKD-EPI}$ = estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = annualized change in estimated GFR using the Modification of Diet in Renal Disease equation; GFR = glomerular filtration rate; SD = standard deviation.

Source: Amicus Therapeutics.[21]

Table 23: GL-3 in Kidney Interstitial Capillaries in the FACETS Trials

	FACETS			
	Migalastat		Placebo	
≥ 50% reduction in the number of GL-3 inclusions per kidney interstitial capillary in Stage 1 (during the double-blind period, month 6)	13/32 (41%)		9/32 (28%)	
P value	0.30			
Median change in interstitial capillary GL-3 from baseline	−40.8%		−5.6%	
P value	0.10			
Mean difference for the change in the percentage of interstitial capillaries with no GL-3 inclusions	7.3 percentage points in favour of migalastat			
P value	0.04			
Change in Mean Number of Kidney Interstitial Capillary GL-3 Inclusions				
Baseline – mITT				
n	30		30	
Mean ± SD	0.922 ± 1.64		0.645 ± 0.80	
Baseline – mITT - patients with amenable mutations				
n	25		20	
Mean ± SD	0.649 ± 1.23		0.493 ± 0.594	
Stage 1 (during the double-blind period), month 6 (mITT - patients with amenable mutations)				
n	26		20	
Mean ± SD	0.389 ± 0.792		0.565 ± 0.975	
Stage 2, month 12 (mITT - patients with amenable mutations)				
n	22		17	
Mean ± SD	0.429 ± 0.861		0.312 ± 0.628	
Change from Baseline in Mean Number of GL-3 Inclusions per Interstitial Capillary in Patients with Amenable Mutation				
Stage 1 (during the double-blind period), Month 6	−0.250 ± 0.103		0.071 ± 0.126	
P value	0.008			
Stage 2, month 12	0.008 ± 0.038		−0.330 ± 0.152	
P value	0.014			
	Males	Females	Males	Females
mITT Population				
Baseline (n)	10	20	12	18
Mean ± SD	2.29 ± 2.24	0.199 ± 0.16	1.02 ± 0.94	0.284 ± 0.19
Median	1.358	0.140	0.910	0.226
Stage 1 (during the double-blind period), Month 6 (n)	10	20	12	18
Mean ± SD	1.812 ± 2.3	0.173 ± 0.15	1.23 ± 1.31	0.273 ± 0.20
Median	0.546	0.106	0.755	0.205
Change from baseline to stage 1 (double-blind period month 6)				
n	10	20	12	18
Mean ± SD	−0.476 ± 0.7992	−0.025 ± 0.1768	0.213 ± 0.7701	−0.011 ± 0.1421
Median	−0.196	−0.005	−0.024	−0.049
Stage 2 Month 12 (n)	7	19	11	15
Mean ± SD	1.834 ± 2.1629	0.188 ± 0.1511	1.331 ± 1.6846	0.165 ± 0.0982

	FACETS			
	Migalastat		Placebo	
Median	0.614	0.130	0.206	0.139
Change from baseline/month 6 to stage 2/month 12[a]				
n	7	19	11	15
Mean ± SD	−0.507 ± 0.9296	−0.006 ± 0.1462	0.004 ±1.22	−0.134 ±0.24
Median	−0.415	−0.030	−0.053	−0.058
mITT-Patients with amenable mutations				
Baseline (n)	7	18	9	11
Mean ± SD	1.787 ± 1.9650	0.206 ± 0.1681	0.701 ± 0.8315	0.324 ± 0.2145
Median	1.218	0.140	0.160	0.291
Stage 1 (during the double-blind period), Month 6 (n)	7	18	9	11
Mean ± SD	0.982 ± 1.4107	0.172 ± 0.1484	0.930 ± 1.3898	0.266 ± 0.2077
Median	0.372	0.106	0.137	0.252
Change from baseline to stage 1 (during the double-blind period) month 6				
n	7	18	9	11
Mean ± SD	−0.805 ± 0.678	−0.034 ± 0.181	0.229 ± 0.828	−0.058 ± 0.109
Median	−1.102	−0.005	0.010	−0.061
Stage 2 Month 12				
n	5	17	8	9
Mean ± SD	1.332 ± 1.587	0.163 ± 0.123	0.477 ± 0.908	0.165 ± 0.122
Median	0.614	0.114	0.096	0.122
Change from baseline/month 6 to stage 2/month 12[a]				
n	5	17	8	9
Mean ± SD	−0.920 ± 0.721	−0.038 ± 0.100	−0.564 ± 0.830	−0.122 ± 0.270
Median	−0.807	−0.060	−0.088	−0.031
mITT-non-Suitable				
Baseline				
n	3	2	3	7
Mean ± SD	3.459 ± 2.825	0.132 ± 0.021	1.956 ± 0.524	0.220 ± 0.140
Median	4.926	0.132	2.170	0.223
Stage 1 (during the double-blind period), month 6				
n	3	2	3	7
Mean ± SD	3.750 ± 3.076	0.187 ± 0.168	2.120 ± 0.318	0.284 ± 0.210
Median	5.261	0.187	2.283	0.197
Change from baseline to stage 1 (during the double-blind period), month 6				
n	3	2	3	7
Mean ± SD	0.291 ± 0.485	0.055 ± 0.147	0.164 ± 0.716	0.064 ± 0.164
Median	0.013	0.055	−0.057	−0.000
Stage 2 Month 12				
n	2	2	3	6
Mean ± SD	3.089 ± 3.69	0.399 ± 0.265	3.608 ± 0.779	0.164 ± 0.056
Median	3.089	0.399	3.306	0.162
Change from baseline/month 6 to stage 2/month 12[a]				
n	2	2	3	6
Mean ± SD	0.525 ± 0.349	0.267 ± 0.244	1.488 ± 0.642	−0.152 ± 0.056
Median	0.525	0.267	1.271	−0.059

GL-3 = globotriaosylceramide; mITT = modified intention-to-treat; SD = standard deviation.

[a] Migalastat displays change relative to baseline. Placebo displays change relative to month 6.

Sources: Germain et al.[10] and NICE Migalastat for treating Fabry disease evaluation report.[7]

Table 24: Echocardiography-Derived Changes in Patients with Amenable Mutations in the ATTRACT Trial

	ATTRACT			
	Migalastat		ERT	
Parameter	**Baseline Mean**	**Change From Baseline to Month 18 (95% CI)**	**Baseline Mean**	**Change From Baseline to Month 18 (95% CI)**
Migalastat: LVMI (g/m^2)				
All (n = 33) (% abnormal)	95.3 (39)	−6.6 (−11.0 to −2.2)[a]		
LVH[b] at baseline (9 females and 4 males)	116.7	−8.4 (−15.7 to 2.6)		
ERT: LVMI (g/m^2)				
All (n = 16) (% abnormal)			92.9 (31)	−2.0 (−11.0 to 7.0)
LVH[b] at baseline (n = 5) (1 female and 4 males)			123.3 (100%)	4.5 (−20.9 to 30.0)
Patients with multi-organ disease at baseline				
LVMI, mean (SD, n)		−7.9 (12.5, n = 26)		−1.5 (15.4, n = 12)
LVMI, mean (SD, n) (LVH at baseline)		−9.6 (10.1, n = 12)		+4.5 (20.4, n = 5)
Patients with mutations associated with classic phenotype				
LVMI, mean (SD, n)		−8.9 (17.5, n = 11)		−5.3 (14.0, n = 5)
LVMI, mean (SD, n) (LVH at baseline)		−11.1 (13.4, n = 4)		−4.7 (16.5, n = 2)
LVMI by gender				
Male		−9.415 (−17.036 to −1.795)		4.05 (−15.362 to 23.462)
Female		−4.529 (−10.301 to 1.244)		−7.213 (−15.889 to 1.463)
Migalastat: LVPWT (cm)				
All (n = 33)	1.17	−0.035 (−0.077 to 0.007)		
ERT: LVPWT (cm)				
All (n = 16)			1.08	0.029 (−0.037 to 0.094)
Migalastat: IVSWT (cm)				
All (n = 33)	1.16	0.058 (−0.200 to 0.140)		
ERT: IVSWT (cm)				
All (n = 16)			1.18	0.037 (−0.051 to 0.124)
Migalastat: left ventricular ejection fraction (% ± SEM) (n = 33)	64.0 ± 0.51	−1.07 ± 0.53		
ERT: left ventricular ejection fraction (% ± SEM) (n = 17)			61.1 ± 1.0	−0.49 ± 1.1

CI = confidence interval; ERT = enzyme replacement therapy; IVSWT = intraventricular septal wall thickness; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; LVPMT = left ventricular posterior wall thickness; LVPWT = left ventricular posterior wall thickness diastolic.
Note: LVMI (g/m^2): normal: female, 43–95, male, 49–115; LVPMT (cm): normal: female, 0.6–< 1.0, male, 0.6–<1.1; IVSWT (cm): normal: female, 0.6–0.9, male, 0.6–1.0.
[a] Statistically significant (95% CI does not overlap zero).
[b] LVH; defined as LVMI (g/m^2) > 95 (females) or > 115 (males).
Sources: Hughes et al.[6] and EMA report.[8]

Table 25: LVMI Changes Between Baseline and Month 6 in the FACETS Trial

	FACETS	
	Migalastat-Migalastat	Placebo-Migalastat
ITT - Patients with amenable mutations		
Baseline		
n	25	19
Mean ± SD	93.3 ± 30	101.7 ± 37
Stage 1 (during the double-blind period), Month 6		
N	27	16
Mean ± SD	92.9 ± 29	108 ± 51
ITT - Patients with non-amenable mutations		
Baseline		
N	5	9
Mean ± SD	83.7 ± 17	92.0 ± 28
Stage 1 (during the double-blind period), Month 6		
N	5	9
Mean ± SD	78.6 ± 15	89.6 ± 28

ITT = intention-to-treat; SD = standard deviation.
Source: Germain et al.[10]

Table 26: Change from Baseline in Plasma Lyso-Gb3 in the ATTRACT and FACETS Trials

	ATTRACT[a]		FACETS[b]	
	Migalastat	ERT	Migalastat	Placebo
Lyso Gb-3 (nmol/L)				
Baseline				
N	32	17	18	13
Mean	9.064	17.648	47.3	41.9
SD	10.8217	20.7824	62	39
SEM	1.913	5.0405	NR	NR
Median	6.345	9.65	NR	NR
Min, max	0.80, 59.07	0.85, 73.40	NR	NR
Treatment Period Month 18				
N	31	15	NA	NA
Mean	11.024	15.846	NA	NA
SD	15.5978	18.6469	NA	NA
SEM	2.8015	4.8146	NA	NA
Median	7.397	6.413	NA	NA
Min, max	1.01, 87.37	0.84, 62.50	NA	NA
Change from Baseline				
N	31	15		
Mean	1.728	−1.926		
SD	5.5332	4.8872		
SEM	0.9938	1.2619		
Median	0.55	−0.043		
Min, max	−2.27, 28.30	−11.90, 2.57		
95% CI	(−0.301 to 3.758)	(−4.632 to 0.781)		

	ATTRACT[a]		FACETS[b]	
	Migalastat	ERT	Migalastat	Placebo
Stage 1 (during the double-blind period), Month 6				
N			18	13
Mean ± SD			36.1 ± 46	42.4 ± 43
Change from Baseline (Mean ± SD)			−11.2 ± 4.8	0.6 ± 2.4
P value			0.003	
Stage 2, Month 12				
N			18	13
Mean ± SD			37.3 ± 50	26.9 ± 22

CI = confidence interval; ERT = enzyme replacement therapy; Lyso-Gb3 = globotriaosylsphingosine; NA = not applicable; NR = not reported; SD = standard deviation; SEM = standard error of mean.
[a] Modified intention-to-treat population.
[b] In patients with amenable mutations.
Sources: Germain et al.[10] and EMA report.[8]

Table 27: Change From Baseline in 24-Hour Urine Protein and 24-Hour Albumin: Creatinine Ratio in the ATTRACT Trial (All mITT)

	ATTRACT[a]	
	Migalastat	ERT
24-Hour Urine: Protein (mg/day)		
Baseline		
n	34	18
Mean	259.6	417.4
SD	422.22	735.46
Median	123.5	171.5
Min, max	0, 2282	0, 3154
Treatment Period Month 18		
n	34	16
Mean	308.8	615.6
SD	525.68	1412.66
SEM		
Median	107.0	143.5
Min, max	0, 2427	0, 5566
Change from Baseline		
n	34	16
Mean	49.2	194.5
SD	199.53	690.77
SEM	NA	NA
Median	0	0
Min, max	–213, 942	–576, 2412
95% CI	–20.412 to 118.824	–-173.583 to 562.583
24-Hour Urine Albumin:Creatinine Ratio (mg/mmol)		
Baseline		
n	33	17
Mean	13.5497	21.888

	ATTRACT[a]	
	Migalastat	**ERT**
SD	28.91233	47.07631
Median	2.5990	5.7630
Min, max	0.339, 155.940	0.452, 196.959
Treatment Period Month 18		
n	33	16
Mean	18.8333	34.9876
SD	38.54475	86.34784
SEM	NA	NA
Median	2.3730	3.2205
Min, max	0.226, 163.737	0.452, 336.514
Change from Baseline		
n	32	15
Mean	5.7771	14.3359
SD	19.66486	40.20133
SEM	NA	NA
Median	0.5650	0
Min, max	–5.763, 109.271	–15.933, 139.555
95% CI	(–1.313 to 12.867)	(–7.927 to 36.599)

CI = confidence interval; ERT = enzyme replacement therapy; SEM = standard error of mean; SD = standard deviation.
[a] Modified intention-to-treat population.
Source: Amicus Therapeutics.[21]

Table 28: Summary of 24-hour Urine Protein ITT Patients with Amenable Mutations in the FACETS Trial

	FACETS			
mg/24-hour	**Migalastat-Migalastat**	**Change From Baseline**	**Placebo-Migalastat**	**Change From Baseline**
Baseline				
n	23		19	
Mean ± SD (median)	268.7 ± 344		655.3 ± 760	
Median	163.0		320.0	
Stage 1 (during the double-blind period), Month 6				
n	28		22	
Mean ± SD	270.8 ± 232	2.2 ± 252	642.4 ± 715	−12.9 ± 224
Median	185.0	15.0	346.0	−9.0
Stage 2, Month 12				
n	22		18	
Mean ± SD	353.7 ± 448	77.1 ± 153	529.7 ± 519	−17 ± 271
Median	158.5	12	369.0	−15

Source: Germain et al.[10]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Brief Pain Inventory (BPI)
- Gastrointestinal Symptom Rating Scale (GSRS)
- Plasma and urine globotriaosylsphingosine (lyso-Gb3)
- Short-Form 36 (SF-36) version 2 (v2)

Findings

Brief Pain Inventory

The BPI was primarily developed and used to assess how cancer pain interferes with or influences patients' lives.[26,27] It has subsequently been accepted and validated as a measure that can assess how pain affects or interferes with the daily functioning in patients with many different diseases and in many health care settings.[26,28,29] The BPI is a self-reporting measure that assesses both pain and how pain affects and interferes with life.[27,29] It is composed of eight questions relating to pain, with four of these questions having a rating scale between 0 and 10, one diagrammatic picture question asks about the pain location, and three other questions pertain to pain and pain relief.[29] For the assessment of pain, the following scores indicate pain severity: a score of 1 to 4 indicates "mild pain," a score of 5 to 6 indicates "moderate pain," and a score of 7 to 10 indicates "severe pain."[26,29] The ninth question is split into seven separate questions, which are grouped to assess three main areas of daily functioning; these include sleep, physical functioning (which includes assessments of general activity, normal work [which includes both house and outside work], and walking ability), and emotional functioning (which includes assessments of life enjoyment, mood, and relationships with others). These Items are also scored between 0 and 10.[27,29]

In a systematic review by Johnston et al.,[38] which examined some commonly used patient-reported outcomes in lysosomal storage diseases, the BPI domains that were the most responsive in patients with Fabry disease (FD) were the "pain on average" and "pain now" domains. The main strengths associated with this systematic review included the explicit eligibility criteria and the focus on instruments that were previously validated and most likely to provide the most reliable results.[38] The limitations associated with this systematic review included the limitations of the primary studies included, reporting on only the last time point of the primary studies (where there could have possibly been changes earlier that were not noted), and having to use the distribution-based minimal clinically important difference (MCID) method from a sample of healthy American adults for the BPI.[38] The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recommends the use of the interference scale of the BPI to ascertain the level of physical functioning in patients who are being assessed for pain (or chronic pain) in clinical trials, unless there is a validated disease-specific measure.[27] There is consensus that any pain scales used to assess pain should have features that assess pain intensity, location of the pain, temporal patterns of pain, the impact of pain on functioning, and quality of pain.

Depending on the pain condition and the treatments examined, changes in the BPI interference scale scores between 1 and 3 points are generally enough to demonstrate an

improvement.[27] Differences in the range of 1 or 2 points have been observed between patients who were satisfied with their treatment (and thus reported lower interference levels) and those whose treatment did not work or who were not satisfied with their treatment.[27] A benchmark for the BPI MCID has been suggested to be a change of 1 point (or 0.5 of its standard deviation) on the interference scale.[27,28] However, no MCID has been identified for patients with FD.

Gastrointestinal Symptom Rating Scale

The GSRS is a patient-reported outcome that was originally designed to ascertain changes in gastrointestinal (GI) symptoms in patients with irritable bowel syndrome (IBS) and peptic ulcer disease (PUD).[30] In its complete form, the GSRS rating scale examines the full range of GI symptoms by including impact on daily living, intensity of symptoms, duration of attacks, and frequency of attacks. However, individual variables can be removed from the scale to ascertain changes within specific indications that may not require the full list.[30]
There are 15 individual variables that examine both upper and lower GI symptoms and they are scored between 0 and 3. These upper GI symptom variables include abdominal pain, heartburn, acid regurgitation, sucking sensation in the epigastrium, nausea and vomiting, borborygmus (abdominal rumbling), abdominal distention, eructation (belching), and increased flatus (passing gas). Scoring for these is determined by the following: 0 = none or transient, 1 = occasional, 2 = prolonged/frequent/troublesome, 3 = severe/continuous .[30]
The lower GI symptom variables include decreased passage of stools (0 = once/day, 1 = every third day, 2 = every fifth day, 3 = every seventh day or less frequently), increased passage of stools (0 = once/day, 1 = three times/day, 2 = five times/day, 3 = seven times/day or more frequently), loose stools, hard stools, (0 = normal, 1 = somewhat, 2 = runny/hard, 3 = watery/hard fragmented), urgent need for defecation (0 = normal, 1 = occasional, 2 = frequent, 3 = inability to control), and feeling of incomplete evacuation (0 = feeling of complete, 1 = somewhat difficult, 2 = definitely difficult, 3 = extremely difficult).[30]

When developing the GSRS, the author did not validate it, mainly due to the fact that there was no control group available.[30]
Inter-rater reliability was assessed by two independent physicians using 20 patients. Weighted kappas indicated that the inter-rater reliability ranged between 0.86 and 1.00 for separate items and 0.92 to 0.94 for the IBS or PUD syndromes, and agreement between raters appeared satisfactory.[30]

In a prospective study of renal transplant patients changing from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPS), the estimated MCIDs (based on a minimal sample size of 102 patients per cohort and to provide 80% power) was 0.6 for abdominal pain, 0.8 for reflux, 0.4 for diarrhea, 0.7 for indigestion, and 0.7 for constipation subscales.[31] However, no MCID was identified for patients with FD.

Lyso-Gb3

Patients with FD experience a deficiency of alpha-galactosidase A (alpha-Gal A) activity, and a consequent accumulation of glycolipids (with the most predominant form being globotriaosylceramide [Gb3]) in the lysosomes.[39] The elevated levels of Gb3 detected in either plasma or urine of male patients with classic FD was formerly used as a biomarker for diagnosis and treatment. However, it was subsequently determined not to be an ideal biomarker, primarily due to the fact that male patients with variant FD and female FD heterozygotes did not necessarily have elevated Gb3.[39]

As the deacylated form of Gb3, lyso-Gb3 has been observed to be increased in the plasma of male patients with classic FD and was subsequently studied in hemizygous patients with variant FD and in heterozygous females. In one observational study that examined patients with various mutations before and during enzyme replacement therapy (ERT) (along with healthy volunteers), hemizygous patients with classic FD had increased levels of lyso-Gb3 that were higher than those patients with the variant form (who still had elevated levels). In heterozygous females, moderately increased lsyo-Gb3 levels were observed in both symptomatic and asymptomatic patients and the levels were correlated with a decrease in alpha-Gal A activity.[39] The main limitation associated with this study is it is observational in nature.[39]

Another observational study examined plasma lyso-Gb3 levels in the entire Dutch cohort of FD patients with classic manifestations of FD (n = 92; hemizygotes and heterozygotes) and healthy controls to determine the ability of lyso-Gb3 to confirm FD diagnosis and its relationship with clinical manifestations.[40] Lyso-Gb3 was confirmed to be useful in the diagnosis of FD as abnormally high concentrations were observed in all hemizygous males and heterozygous female FD patients and was distinguishable from plasma levels from healthy volunteers. In addition, individuals carrying a nucleotide change in their alpha-Gal A gene that is not unequivocally linked to FD did not have elevated plasma lyso-Gb3, indicating this biomarker as an appropriate additional assessment for FD confirmation.[40]

Plasma lsyo-Gb3 has been observed to be particularly useful for diagnosing females with FD as they do not always present with the same symptoms.[41,42] However, in female patients who are later-onset heterozygotes, the lyso-Gb3 levels may be low and not as effective as a biomarker (possibly due to X-chromosomal deactivation).[42] In terms of any correlation with clinical manifestations, it appears that high lyso-Gb3 exposure is an independent risk factor for white matter lesions in male FD patients and for LVH in females.[40] It is presently even thought to potentially play a direct pathogenic role in FD.[40,41] While there is potential for the use of plasma lyso-Gb3 in monitoring disease progression during the treatment of FD patients with ERT, one study did observe the loss of its reliability as a therapeutic measure during ERT treatment specifically in Chinese FD patients with the IVS4+919G>A mutation.[43]

An observational laboratory study examined the urinary levels of lyso-Gb3 in patients with FD (with various mutational types; n = 83) and healthy volunteers (n = 77).[22] Time-to-flight mass spectrometry was used to measure the lyso-Gb3 (which was validated as accurate and precise).[22] No lyso-Gb3 was observed in any of the urine from healthy volunteers, while there were significant correlations observed between lyso-Gb3/creatinine and ERT status, different mutational types (suggesting predictive value in clinical severity), and age.[22] Urine lyso-Gb3 was determined not to be a good predictor for kidney involvement as there was no correlation observed with estimated glomerular filtration rate (eGFR).[22]

No MCID in either plasma or urine lyso-Gb3 has been identified.

Short-Form 36 v2

The SF-36 (with version 2 being the most up-to-date version) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[23] The SF-36 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[23-25] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summaries (PCS) and the mental

component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status.[23,24] The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation (SD) of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population.

The SF-36 has been validated in a variety of disease conditions.[25,44,45] A systematic review with subsequent meta-analysis by Arends et al.[28] was able to detect that, when compared with the general population, patients with FD scored worse across every domain of the SF-36.[28] The EuroQol 5-Dimensions questionnaire (EQ-5D, another general health status instrument) also demonstrated this same conclusion.[28] With the exception of the mental health domain, significant differences were observed in patients with FD whose eGFR was both greater than/less than 60 mL/min/1.73 m^2, indicating that the SF-36 can differentiate between patients with varying disease severity (particularly in terms of renal function).[28] Again the EQ-5D echoed these findings.[28] Increasing age in patients with FD has been observed to be associated with a lower quality of life, with males deteriorating earlier than females (based on the Fabry Registry). The SF-36 was able to differentiate between the age of FD patients, as the males between the ages of 18 and 25 had lower scores in six out of the eight subdomains. Conversely, females of the same age were reported to have normal scores except in the subscales of bodily pain and general health.[28] When patients above the age of 25 were assessed with the SF-36, both sexes exhibited reductions in their quality of life, particularly in the bodily pain, physical functioning, vitality, and general health subdomains. As a result, the SF-36 can differentiate on the age-related quality of life in patients with FD.[28] The SF-36 (along with the EQ-5D) was determined to be responsive (when primarily examined in retrospective cohort studies of primarily treatment-naive patients with FD), with the general health, vitality, and mental health domains appearing to be the most responsive.[38] There is inconclusive evidence to state that the SF-36 is effective in showing any effect of ERT on quality of life in the systematic review by Arends et al.[28] There were significant limitations in of the primary studies included in the systematic review that potentially may have affected the assessment of the SF-36 on ERT. However, this same inconclusiveness was evident when other studies were examined.[38]

On any of the scales, an increase in score indicates improvement in health status. In general use, a change of 2 points in the SF-36 PCS and 3 points in the SF-36 MCS indicates a clinically meaningful improvement as determined by the patient.[46] Based on anchor data, the SF-36 User's Manual also proposed the following minimal mean group differences, in terms of T-score points, for SF-36v2 individual dimension scores: physical functioning, 3; role physical, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3. It should be noted that these minimally important difference (MID) values were determined as appropriate for groups with mean T-score ranges of 30 to 40. For higher T-score ranges, MID values may be higher.[46] In other citations, the MCID for either the PCS or MCS of the SF-36 has been determined to be typically between 2.5/3 and 5 points.[24,44,45] No specific MCID or MCID range has been specifically determined for patients with FD.

Table 29: Validity and MCID of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
BPI	Instrument that assesses how pain interferes with or influences a patient's life (particularly emotional functioning, physical functioning, and sleep)	Yes	1 point or 0.5 of its SD	Arends 2015[28] Dworkin 2008[27]
GSRS	15-item Instrument that assesses frequency, intensity, duration, and impact on daily lives of both upper and lower GI symptoms	No	0.6 for abdominal pain, 0.8 for reflux, 0.4 for diarrhea, 0.7 for indigestion, and 0.7 for constipation subscales	Chan 2006[31] Svedlund 1988[30]
Lyso-Gb3	Plasma or urine biomarker used to diagnose and observe disease progression	Yes	No	Aerts 2011[41] Auray-Blais 2010[22] Nowak 2017[42] Togawa 2010[39]
SF-36	General health status instrument that contains a PCS and MCS	Yes	2 points in SF-36 PCS 3 points in SF-36 MCS[a]	Maruish, 2011[46]

BPI = Brief Pain Inventory; GI = gastrointestinal; GSRS = Gastrointestinal Symptom Rating Scale; Lyso-Gb3 = globotriaosylsphingosine; MCS = mental component summary; PCS = physical component summary; SD = standard deviation; SF-36 = Short-Form 36-Item Health Survey.

Note: Nothing appeared in the literature search results for the SF-36 v2.

[a] This is not specific for patients with Fabry disease.

Conclusion

When compared with the general population, patients with FD scored lower across every domain in the SF-36. In addition, the SF-36 correlated with both disease severity and age and is a responsive measure in patients with FD (especially in the general health, vitality, and mental health domains). However, there is inconclusive evidence pertaining to the correlation of the SF-36 with the effectiveness of ERT. The BPI domains that were the most responsive in patients with FD were the "pain on average" and "pain now" domains. The IMMPACT group recommends the use of the interference scale of the BPI to ascertain the level of physical functioning in patients that are being assessed for pain (or chronic pain) in clinical trials, unless there is a validated disease-specific measure (of which none were used in the ATTRACT or FACETS clinical trials). The plasma lyso-Gb3 biomarker is effective at diagnosing hemizygote and variant males and heterozygous females who are both symptomatic and asymptomatic. The GSRS was originally designed for patients with IBS and PUD and has satisfactory inter-rater reliability, but there is no evidence of its validity in patients with FD.

While in general use, a change of 2 points in the SF-36 PCS and 3 points in the SF-36 MCS indicates a clinically meaningful improvement as determined by the patient, but there was no evidence identified to support this in patients with FD. A benchmark for the BPI MCID has been suggested to be a change of 1 point, or 0.5 of its standard deviation, on the interference scale. No MCID in either plasma or urine lyso-Gb3 have been identified. The MCID for the GSRS has been estimated at 0.6 for abdominal pain, 0.8 for reflux, 0.4 for diarrhea, 0.7 for indigestion, and 0.7 for constipation subscales. However, this was determined in a cohort of patients with renal transplant patients changing from MMF to EC-MPS.

Appendix 6: Summary of Open-Label Extension Studies

Objective

To summarize the efficacy and safety results of the optional 12-month open-label extensions (OLE) of the ATTRACT trial[19] and FACETS trials.[20] The following summary is based on unpublished data from the clinical study reports from both trials.

Trial Description

ATTRACT Open-Label Extension

Patients who had completed the 18-month randomized period of ATTRACT were able to participate in an optional 12-month OLE, whereby all patients received migalastat. Period 1 (18-month randomization treatment period) lasted approximately 33 months while period 2 (optional 12-month OLE period) lasted approximately 30 months. Those patients who were originally randomized to the migalastat group continued taking migalastat (migalastat-migalastat group). Patients who were originally randomized to the enzyme replacement therapy (ERT) group discontinued ERT and started treatment with migalastat (ERT-migalastat). The OLE population consisted of all patients who took at least one dose of migalastat during the OLE and agreed to participate. All patients took migalastat 150 mg orally every other day and inactive reminder capsules on the alternating days, all taken at approximately the same time every day. Analyses were performed according to all randomized patients and those with amenable mutations. The planned 30-month analyses included (but were not limited to) kidney/renal function (annualized rate of change in measured glomerular filtration rate as assessed by plasma clearance of iohexol [$mGFR_{iohexol}$] and estimated glomerular filtration rate [eGFR]), cardiac function (reduction in left ventricular mass index [LVMI], left ventricular mass [LVM], intraventricular septum thickness diastolic, left ventricular fractional shortening, left ventricular ejection fraction [LVEF], and left ventricular posterior wall thickness [LVPWT]), substrate/laboratory levels (plasma lyso-Gb3, 24-hour urine protein), patient-reported outcomes (Short-Form 36-Item Health Survey [SF-36 v2] and questions based on Brief Pain Index (BPI) pain severity component) and long-term safety. No statistical inference testing was performed and all analyses were performed with descriptive statistics. Where appropriate, two-sided 95% confidence intervals (CIs) were provided for summary purposes.

FACETS OLE

Patients who had completed both stage 1 and stage 2 of the main FACETS study were eligible to participate in the 12-month OLE phase, whereby patients continued to take 150 mg every other day for up to 12 months and underwent a follow-up visit one month after their last dose of migalastat. The total duration of stage 1, stage 2, and the OLE was 24 months. Efficacy outcomes of interest in the OLE included eGFR by the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD-EPI}$), $mGFR_{iohexol}$, estimated GFR by the Modification of Diet in Renal Disease equation ($eGFR_{MDRD}$), LVMI, SF-36 v2, questions based on the BPI pain severity component, Gastrointestinal Symptoms Rating Scale, and plasma globotriaosylsphingosine . The data for white blood cell alpha-galactosidase A (alpha-Gal A) activity was analyzed for male patients only. No statistical inference testing was performed; instead all analyses were performed with descriptive statistics.

Results

Details regarding the patient disposition are presented in Table.

With regard to the ATTRACT OLE population, 31 (86%) and 15 (63%) patients with amenable mutations entered with 30 (97%) and 12 (80%) completing the 12-month OLE period in the migalastat-migalastat and ERT-migalastat groups, respectively.

In the FACETS trial, a total of 57 patients completed stage 2 and entered the OLE, of which 29 patients were in the migalastat-migalastat group and 28 patients were in the placebo-migalastat group. Twenty-seven (93%) and 27 (96%) patients in the migalastat-migalastat and placebo-migalastat groups, respectively, discontinued during the OLE.

Table 30: Patient Disposition for ATTRACT and FACETS 12-Month OLE

	ATTRACT		FACETS	
Parameter	**Migalastat-Migalastat[a]**	**ERT-Migalastat[b]**	**Migalastat-migalastat**	**PL-Migalastat**
Patients randomized in OLE population, N	36	24	34	33
Patients with amenable mutations in the OLE population, n (%)	31 (86)	15 (63)	29 (85)	28 (85)
Completed 12-month OLE period, n (%)	30 (97)	12 (80)	27 (93)	27 (96)
Discontinued during 12-month OLE period (as per eCRF), n (%)	1 (3)	3 (20)	2 (7)	1 (4)
AEs	0	0	1 (3)	1 (3)
Physician's decision	0	1 (6.7)	0	0
Lost to follow-up	0	1 (6.7)	1 (3)	0
Pregnancy	1 (3.2)	0	1 (3)	1 (3)
Withdrawal by patient	0	1 (6.7)	2 (6)	3 (9)
Patients in ITT Population, n (%)	33 (92)	15 (63)	-	-
Patients in OLE Population, n (%)	33 (92)	15 (63)	-	-
Patients in the Safety Population, n (%)	-	-	34	33

AE = adverse event; eCRF = electronic case report form; ERT = enzyme replacement therapy; ITT = intention-to-treat; OLE = open-label extension; PL = placebo.
[a] The migalastat-migalastat group includes subjects who received migalastat during the 18-month randomized treatment period and continued on migalastat during the 12-month OLE period.
[b] The ERT-migalastat group includes subjects who received ERT during the 18-month randomized treatment period and switched to migalastat during the 12-month OLE period.
[c] Percentages are based on the number of patients in the Safety Population and reasons for discontinuations were recorded at any time during the study.
Sources: ATTRACT Clinical Study Report[19] and FACETS Clinical Study Report.[20]

Patient Characteristics

Detailed patient characteristics are provided in Table 29, with groups similar for most of the patient and disease characteristics. Most parameters were similar between groups with the exception of mean 24-hour protein in the ATTRACT OLE (with patients in the migalastat-migalastat group having a lower mean amount that that of the ERT-migalastat group) and a higher percentage of patients in the placebo-migalastat group (compared with the migalastat-migalastat group) using angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/renin inhibitor in the FACETS OLE.

Table 29: Summary of Baseline Characteristics (OLE Population)

	ATTRACT[a]		FACETS[b]	
Parameter	**Migalastat-Migalastat N = 33**	**ERT-Migalastat N = 15**	**Migalastat-Migalastat N = 34**	**PL-Migalastat N = 33**
Age (years)				
Mean (SD)	50.3 (14.37)	45.3 (15.69)	40 (13.29)	44.5 (10.18)
Sex, n (%)				
Male	16 (48)	5 (33)	12 (35)	12 (36)
Female	17 (52)	10 (67)	22 (65)	21 (64)
Years since diagnosis, mean (SD)	10.6 (12.16)	16.1 (13.62)	5.7 (6.76)	7. 1 (7.84)
24-hour protein (mg/24 hours)				
Mean (SD)	276.1 (427.23)	372.6 (800.51)	NR	NR
$mGFR_{iohexol}$ (mL/min/1.73 m²)				
Mean (SD)	82.84 (18.800)	81.18 (25.908)	NR	NR
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)				
Mean (SD)	90.589 (22.8936)	96.045 (20.9965)	95.4 (28.51)	93.8 (20.64)
ERT at baseline, n (%)				
Agalsidase beta	10 (30)	5 (33)	5 (15)[c]	12 (36)
Agalsidase alfa	22 (67)	10 (67)		
$eGFR_{MDRD}$ (mL/min/1.73 $m^{2)}$ Mean (± SD)	84.8 (22.33)	86.4 (19.39)	NR	NR
Left ventricular mass index (g/m^2)	22 (67)	10 (67)	NR	NR
Use of ACEI/ARB/RI, n (%)	15 (45)	7 (47)	6 (18)	13 (39)
Amenable GLA mutation, n (%)	31 (94)	15 (100)	29 (85)	28 (85)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = estimated glomerular filtration rate assessed by the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GLA = gene encoding alpha-galactosidase A; $mGFR_{iohexol}$ = measured glomerular filtration rate as assessed by plasma clearance of iohexol; NR = not reported; OLE = open-label extension; PL = placebo; RI = renin inhibitor; SD = standard deviation.

[a] Demographic characteristics recorded at the beginning of the 18-month randomized treatment period.

[b] Demographics were based on the safety population and not separated out for the OLE.

[c] Presented as number of patients previously on ERT.

Sources: ATTRACT Clinical Study Report[19] and FACETS Clinical Study Report.[20]

Efficacy Results

Renal Outcomes

Detailed annualized rates of change are provided in Table 30.

In patients with amenable mutations in the migalstat-migalastat group in the ATTRACT trial, the mean annualized rate of change in $eGFR_{CKD-EPI}$ from baseline to month 30 was statistically significant at –1.7 mL/min/1.73 m^2 (95% CI, –2.7 to -0.8 mL/min/1.73 m^2). The mean annualized rate of change of $mGFR_{iohexol}$ for the same time point was statistically significant at –2.746 mL/min/1.73 m^2 (95% CI, –4.812 to –0.681 mL/min/1.73 m^2), while the mean annualized rate of change of $eGFR_{MDRD}$ for the same time point was also statistically significant at –2.281 mL/min/1.73 m^2 (95% CI, –3.984 to –0.578 mL/min/1.73 m^2).

The $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and $mGFR_{iohexol}$ were examined in the OLE; however, the mean annualized changes were presented for the overall population, rather than presenting them per treatment group. The mean annualized change for $eGFR_{CKD-EPI}$ was –0.30 mL/min/1.73 m^2 (standard error of the mean [SEM] of 0.663 mL/min/1.73 m^2, for $eGFR_{MDRD}$ was 0.79 mL/min/1.73 m^2 (SEM of 1.027 mL/min/1.73 m^2), and for $mGFR_{iohexol}$ was –1.51 mL/min/1.73 m^2 (SEM of 1.327 mL/min/1.73 m^2.

Table 30: Annualized Rate of Change in $eGFR_{CKD-EPI}$, $mGFR_{iohexol}$, $eGFR_{MDRD}$ (OLE Population Excluding Patients With Non-Amenable Mutations)

	ATTRACT		FACETS	
Parameter	**Migalastat-Migalastat N = 31**	**ERT-Migalastat N = 15**	**Migalastat-Migalastat**	**PL-Migalastat**
Annualized Rate of Change in $eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)				
Baseline – Month 18 Mean (SD) 95% CI	 –1.069 (3.1159) –2.212 to 0.074	 –2.039 (6.6534) –5.723 to 1.646	-	-
Baseline – Month 30 Mean (SD) 95% CI	 -1.718 (2.5501) –2.653 to –0.782	-	n = 41 –0.30 (0.663)[a] NR	
Month 18 – Month 30 Mean (SD) 95% CI	 2.664 (11.7280) –1.638 to 6.966	 –2.131 (12.4299) –9.015 to 4.752	-	-
Annualized Rate of Change in $mGFR_{iohexol}$ (mL/min/1.73 m^2)				
Baseline – Month 18 Mean (SD) 95% CI	 4.979 (9.5356) (–8.476 to –1.481)	 –0.653 (9.3691) (–5.842 to 4.535)	-	-
Baseline – Month 30, n Mean (SD) 95% CI	30 –2.746 (5.5318) (–4.812 to –0.681)	-	37 –1.51 (1.327)[a] NR	
Month 18 – Month 30, n Mean (SD) 95% CI	30 0.725 (12.9834) (–4.123 to 5.573)	9 –3.857 (15.0913) (–15.457 to 7.743)	-	-
Annualized Rate of Change in $eGFR_{MDRD}$ (mL/min/1.73 m^2)				
Baseline – Month 18, n Mean (SD) 95% CI	31 –2.156 (4.5737) (–3.834 to –0.479)	15 –2.352 (6.6344) (–6.026 to 1.322)	-	-
Baseline – Month 30, n Mean (SD) 95% CI	31 –2.281 (4.6418) (–3.984 to –0.578)	-	41 0.79 (1.027)[a] NR	
Month 18 – Month 30, n Mean (SD) 95% CI	31 4.959 (24.1666) (–3.905 to 13.824)	15 –1.966 (11.8854) (–8.548 to 4.616)	-	-

CI = confidence interval; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = estimated glomerular filtration rate assessed by the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; $mGFR_{iohexol}$ = measured glomerular filtration rate as assessed by plasma clearance of iohexol; NR = not reported; OLE = open-label extension; SD = standard deviation; SEM = standard error of the mean.

[a] Presented as mean (standard error of the mean). In addition, the values were for 18 months (PL-migalastat) and 24 months (migalastat-migalastat) with the value given representing all patients together.

Sources: ATTRACT Clinical Study Report[19] and FACETS Clinical Study Report.[20]

Renal Outcomes by Subgroups

In the ATTRACT trial, the mean annualized rates of change in $eGFR_{CKD-EPI}$, $mGFR_{iohexol}$, and/or $eGFR_{MDRD}$ were presented by sex based on baseline proteinuria subgroups (Table 31) and baseline $eGFR_{CKD-EPI}$ subgroups (Table 32).

In the FACETS trial, the mean annualized rates of change in $eGFR_{CKD-EPI}$, $mGFR_{iohexol}$, and/or $eGFR_{MDRD}$ were presented by sex and were based on baseline proteinuria subgroups (Table 31).

Table 31: Annualized Rate of Change of $eGFR_{CKD-EPI}$ – Baseline Proteinuria Subgroup Summary (OLE Population Excluding Subjects With Non-Amenable Mutations)

	ATTRACT		FACETS	
	Migalastat-Migalastat Treatment Group		OLE Population Group	
Parameter	**Males**	**Females**	**Males**	**Females**
Patients with amenable mutations, N	14	17	14	27
Annualized Rate of Change in $eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)				
All, n Months 0-30, mean (SD)	14 –2.065 (1.9983)	17 –1.431 (2.9591)	14 –0.96 (1.013)[a]	27 0.093 (0.865)[a]
24-Hour Urine Protein < 100 mg/24 hours n Months 0-30, mean (SD)	7 –2.205 (1.6516)	7 –1.882 (3.4885)	0 -	7 0.22 (1.400)[a]
24-Hour Urine Protein ≥ 100 mg/24 hours n Months 0-30, mean (SD)	7 –1.925 (2.4245)	10 –1.116 (2.6805)	NR	NR
24-Hour Urine Protein ≥ 100 mg/24 hours and <1,000 mg/24 hours n Months 0-30, mean (SD)	6 –1.276 (1.8745)	10 –1.116 (2.6805)	12 –0.03 (0.895)[a]	18 0.16 (1.178)[a]
24-Hour Urine Protein ≥ 1,000 mg/24 hours n Months 0-30, mean (SD)	1 –5.820 (NA)	0 -	2 –6.54 (2.049)[a]	2 –1.78 (2.364)[a]
Annualized Rate of Change in $mGFR_{iohexol}$ (mL/min/1.73 m^2)				
All, n Months 0-30, mean (SD)	14 –1.046 (5.7374)	16 –4.234 (5.0570)	12 –2.98 (1.561)[a]	25 –0.81 (1.819)[a]
24-Hour Urine Protein < 100 mg/24 hours n Months 0-30, mean (SD)	7 –2.576 (4.8978)	6 –2.553 (3.9996)	0 -	7 3.53 (2.898)[a]
24-Hour Urine Protein ≥ 100 mg/24 hours n Months 0-30, mean (SD)	7 0.484 (6.4711)	10 –5.243 (5.5426)	NR	NR
24-Hour Urine Protein ≥ 100 mg/24 hours and < 1,000 mg/24 hours n Months 0-30, mean (SD)	6 1.568 (6.3544)	10 –5.243 (5.5426)	11 –3.25 (1.683)[a]	17 –2.84 (2.278)[a]
24-Hour Urine Protein ≥ 1,000 mg/24 hours n Months 0-30, mean (SD)	1 –6.021 (-)	0 -	1 0.07 (-)[a]	1 3.46 (-)[a]

	ATTRACT		FACETS	
	Migalastat-Migalastat Treatment Group		OLE Population Group	
Parameter	**Males**	**Females**	**Males**	**Females**
Annualized Rate of Change in $eGFR_{MDRD}$ (mL/min/1.73 m^2)				
24-Hour Urine Protein < 100 mg/24 hours n Months 0-30, mean (SD)	 7 –3.282 (2.7664)	 7 –2.031 (8.4931)	 0 -	 7 0.26 (1.385)[a]
24-Hour Urine Protein ≥ 100 mg/24 hours and < 1,000 mg/24 hours n Months 0-30, mean (SD)	 6 –2.181 (3.2172)	 10 –1.511 (3.2176)	 12 0.99 (1.432)[a]	 18 1.84 (2.012)[a]
24-Hour Urine Protein ≥ 1,000 mg/24 hours n Months 0-30, mean (SD)	 1 –5.330 (-)	 0 -	 2 –5.88 (1.750)[a]	 2 –1.25 (2.789)[a]

$eGFR_{CKD-EPI}$ = estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$ = estimated glomerular filtration rate assessed by the Modification of Diet in Renal Disease equation; $mGFR_{iohexol}$ = measured glomerular filtration rate as assessed by plasma clearance of iohexol; OLE = open-label extension; NR = not reported; SD = standard deviation.
[a] Presented as mean (standard error of the mean). In addition, these are month 24 values.
Note: Post hoc analyses.
Sources: ATTRACT Clinical Study Report[19] and FACETS Clinical Study Report.[20]

Table 32: Annualized Rate of Change of $eGFR_{CKD-EPI}$, $mGFR_{iohexol}$ – Baseline $eGFR_{CKD-EPI}$ Subgroup Summary for the ATTRACT trial (Migalastat-Migalastat; OLE Population Excluding Subjects With Non-Amenable Mutations)

Parameter	Migalastat-Migalastat Treatment Group
Patients with Amenable Mutations, N	31
Annualized Rate of Change in $eGFR_{CKD-EPI}$	
Baseline $eGFR_{CKD-EPI}$ 30 to < 60 mL/min/1.73 m^2	
n Baseline - Month 30, mean (SD) 95% CI	2 –3.901 (2.7140) (–28.285 to 20.484)
Baseline $eGFR_{CKD-EPI}$ ≥ 60 to < 90 mL/min/1.73 m^2	
n Baseline - Month 30, mean (SD) 95% CI	15 –1.136 (2.4495) (–2.492 to 0.221)
Baseline $eGFR_{CKD-EPI}$ ≥ 90 mL/min/1.73 m^2	
n Baseline - Month 30, mean (SD) 95% CI	14 –2.029 (2.5981) (–3.529, –0.529)
Annualized Rate of Change in $mGFR_{iohexol}$	
Baseline $eGFR_{CKD-EPI}$ 30 to < 60 mL/min/1.73 m^2	
n Baseline - Month 30, mean (SD) 95% CI	2 –4.348 (2.3648) (–25.596 to 16.899)
Baseline $eGFR_{CKD-EPI}$ ≥ 60 to < 90 mL/min/1.73 m^2	
n	15

Parameter	Migalastat-Migalastat Treatment Group
Baseline - Month 30, mean (SD) 95% CI	–2.104 (4.9969) (–4.871 to 0.663)
Baseline $eGFR_{CKD-EPI} \geq 90$ mL/min/1.73 m^2	
n Baseline - Month 30, mean (SD) 95% CI	13 –3.241 (6.5687) (–7.211 to 0.728)

CI = confidence interval; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation;
$eGFR_{CKD-EPI}$ = estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation;
SD = standard deviation.
Note: Post hoc analyses.
Source: ATTRACT Clinical Study Report.[19]

Other Laboratory Outcomes

Detailed information pertaining to the laboratory parameters are provided in Table 33.

In the ATTRACT trial, the mean change in 24-hour urine protein from baseline to month 30 was smaller (but not statistically significant) in the migalastat-migalastat group (70.2 mg/day; 95% CI, –32.4 to 172.7 mg/day) when compared with the ERT-migalastat group (272.9 mg/day; 05% CI, –223.0 to 768.7 mg/day). Mean change in lyso-Gb3 from baseline to month 30 was lower in the migalastat-migalastat group (3.570 nmol/L; 95% CI, –1.545 to 8.685 nmol/L) when compared with the ERT-migalastat group (3.894 nmol/L; 95% CI, –2.278 to 10.067 nmol/L). However, these changes were not statistically significant.

In the FACETS trial, the mean change in 24-hour urine protein from baseline (migalastat-migalastat group) or month 6 (placebo-migalastat group) were 139.3 mg/day and 257.4 mg/day, respectively. No data were provided for the Lyso-Gb3 outcome in the Clinical Study Report for the OLE of the FACETS trial.

Table 33: Change From Baseline in 24-Hour Urine Protein, and Lyso-Gb3, (OLE Population Excluding Subjects With Non-Amenable Mutations)

	ATTRACT		FACETS	
Parameter	**Migalastat-Migalastat N = 31**	**ERT-Migalastat N = 15**	**Migalastat-Migalastat**	**PL-Migalastat**
24-Hour Urine: Protein (mg/day)				
Baseline				
n Mean (SD)	31 268.6 (440.13)	15 372.6 (800.51)	-	-
Treatment Period Month 30				
Actual n Mean (SD)	 29 350.4 (350.4)	 14 672.1 (1603.46)	-	-
Change From Baseline n Mean (SD) 95% CI	 29 70.2 (269.54) (–32.4 to 172.7)	 14 272.9 (858.75) (–223.0 to 768.7)	139.3 (NR)[a]	257.4 (NR)[b]
Lyso-Gb3 Average by Time Point (nmol/L)				
Baseline				
n	31	15	NR	NR

	ATTRACT		FACETS	
Parameter	**Migalastat-Migalastat N = 31**	**ERT-Migalastat N = 15**	**Migalastat-Migalastat**	**PL-Migalastat**
Mean (SEM)	9.147 (1.9739)	13.607 (4.1022)		
OLE Period Month 30				
Actual n Mean (SEM)	 29 13.107 (4.3988)	 9 16.641 (6.6274)	NR	NR
Change From Baseline n Mean (SEM) 95% CI	 29 3.570 (2.4971) (–1.545 to 8.685)	 9 3.894 (2.6769) (–2.278 to 10.067)	NR	NR

CI = confidence interval; ERT = enzyme replacement therapy; lyso-Gb3 = globotriaosylsphingosine; NR = not reported; OLE = open-label extension; PL = placebo; SD = standard deviation; SEM = standard error of the mean.
[a] Increases observed from baseline (visit 1) to month 24 (visit 10).
[b] Increases observed from month 6 (visit 4) to month 24 (visit 10).
Sources: ATTRACT Clinical Study Report[19] and FACETS Clinical Study Report.[20]

Composite Clinical Outcomes

Detailed descriptions of composite clinical outcomes are provided in Table 34.

Between baseline and month 30 in the ATTRACT trial, nine (29%) and one (3%) patients in the migalastat-migalastat group had renal and cardiac events, respectively. During the 18- to 30-month period, six (40%) and one (7%) patients in the ERT-migalastat groups had renal and cardiac events, respectively. There were no deaths in either group.

Table 34: Composite Clinical Outcome (OLE Population Excluding Subjects With Non-Amenable Mutations)

	ATTRACT	
Parameter	**Migalastat-Migalastat N = 31**	**ERT-Migalastat N = 15**
Renal Event, n (%)		
Months 0-18	6 (19)	4 (27)
Months 18-30	-	6 (40)
Months 0-30	9 (29)	-
Cardiac Event, n (%)		
Months 0-18	1 (3)	3 (20)
Months 18-30	-	1 (7)
Months 0-30	1 (3)	-
Cerebrovascular Event, n (%)		
Months 0-18	0	1 (7)
Months 18-30	-	0
Months 0-30	0	-
Death, n (%)		
Months 0-18	0	0
Months 18-30	-	0
Months 0-30	0	-

ERT = enzyme replacement therapy; OLE = open-label extension.
Source: ATTRACT Clinical Study Report.[19]

Echocardiographic Outcomes

In the ATTRACT trial, mean decreases in left ventricular mass index (LVMI) at month 30 (when measured from baseline) were non-statistically significantly larger in the migalastat-migalastat group (–3.772 g/m^2; 95% CI, –8.873 to 1.328 g/m^2). The mean decreases in LVMI were smaller and not statistically significant in the ERT-migalastat group (–0.629 g/m^2; 95% CI, –8.259 to 7.001 g/m^2. In patients with LVH at baseline, the mean decreases in LVMI in the migalastat-migalastat group were statistically significant according to the 95% CIs (–10.0 g/m^2; 95% CI, –16.6 to –3.3 g/m^2). However, the same decrease was not observed in the ERT-migalastat group (3.9 g/m^2; 95% CI, –33.6 to 41.4 g/m^2). When looking at the male and female subgroup analysis for the migalastat-migalastat group, the decreases were larger in the males (–5.700 g/m^2; 95% CI, –12.697 to 1.297 g/m^2) than the females (–2.525 g/m^2; 95% CI, –10.151 to 5.101 g/m^2); although these were not statistically significant and the sample size was small. Mean changes with accompanying 95% CIs were provided for left ventricle posterior wall thickness (LVPWT), intraventricular septal wall thickness (IVSWT), and LVEF, with only the LVEF being statistically significant for its decrease from baseline to month 30 in the migalastat-migalastat group (–1.219; 95% CI, –2.424 to –0.013). Detailed echocardiography-derived changes are provided in Table 35. In the FACETS trial, in patients with amenable mutations, LVMI was statistically significantly reduced after 18 or 24 months of migalastat treatment (–7.7 g/m^2; 95% CI, –15.4 to –0.01). In patients with LVH, the reduction in LVMI was larger after 18 or 24 months of migalastat treatment (-18.6 g/m^2; 95% CI, –38.2 to 1). However, this change was not statistically significant.[10]

Table 35: Echocardiography-Derived Changes (OLE Population Excluding Subjects With Non-Amenable Mutations)

	ATTRACT	
Parameter	**Migalastat-Migalastat N = 31**	**ERT-Migalastat N = 15**
LVMi (g/m^2): OLE Period Month 30		
Actual: Baseline, n Mean (SD)	 30 94.649 (22.4222)	 13 88.507 (25.6429)
Actual: Month 30 n Mean (SD)	 29 89.266 (20.2636)	
Change from Baseline at Month 30 n Mean (SD) 95% CI	 28 –3.772 (13.1540) (–8.873 to 1.328)	 8 –0.629 (9.1264) (–8.259 to 7.001)
LVMI (g/m^2) by Sex Subgroup		
Baseline		
Actual - Males n Mean (SD)	 13 103.119 (27.6869)	 - -
Actual - Females n Mean (SD)	 17 88.172 (15.2791)	 - -
OLE Period Month 30		
Actual - Males		

	ATTRACT	
Parameter	**Migalastat-Migalastat N = 31**	**ERT-Migalastat N = 15**
n Mean (SD)	12 94.393 (21.9418)	- -
Actual - Females n Mean (SD)	17 85.646 (18.8133)	- -
Change From Baseline - Males n Mean (SD) 95% CI	11 –5.700 (10.4146) (–12.697 to 1.297)	- - -
Change From Baseline - Females n Mean (SD) 95% CI	17 –2.525 (14.8320) (–10.151 to 5.101)	- - -
IVSWT (cm): OLE Period Month 30		
Actual: Baseline, n Mean (SD)	30 1.164 (0.3006)	13 1.116 (0.4764)
Actual: Month 30 n Mean (SD)	31 1.209 (0.3970)	13 1.104 (0.3125)
Change from Baseline at Month 30 n Mean (SD) 95% CI	30 0.045 (0.2748) (–0.057 to 0.148)	11 –0.095 (0.2375) (–0.254 to 0.065)
LVPWT (cm): OLE Period Month 30		
Actual: Baseline, n Mean (SD)	30 1.170 (0.2519)	13 1.029 (0.2585)
Actual: Month 30 n Mean (SD)	31 1.113 (0.2806)	13 1.072 (0.2373)
Change from Baseline at Month 30 n Mean (SD) 95% CI	30 –0.046 (0.1582) (–0.105 to 0.013)	11 –0.002 (0.1259) (–0.086 to 0.083)
LVEF (%); OLE Period Month 30		
Actual: Baseline, n Mean (SD)	30 64.159 (2.7166)	14 61.011 (4.6802)
Actual: Month 30 n Mean (SD)	29 62.926 (3.5055)	10 62.638 (4.3728)
Change from Baseline at Month 30 n Mean (SD) 95% CI	28 –1.219 (3.1090) (–2.424 to –0.013)	9 0.831 (3.9196) (–2.182, 3.844)

CI = confidence interval; ERT = enzyme replacement therapy; IVSWT = intraventricular septal wall thickness; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; LVPMT = left ventricular posterior wall thickness; LVPWT = left ventricular posterior wall thickness diastolic; OLE = open-label extension; SD = standard deviation.

Source: ATTRACT Clinical Study Report.[19]

Patient-Reported Outcomes

Between baseline and month 30 in the ATTRACT trial, no statistically significant improvements in the SF-36 v2 physical or mental components or the BPI were observed in either the migalastat-migalastat or ERT-migalastat groups (Table 36).

In the FACETS trials, mean increases of 4.0 and 4.5 were observed in all patients in the vitality domain and general health domain, respectively (Table 36). Statistically significant (based on the lack of overlap with zero in the 95% CIs) mean improvements were observed in the combined group for the diarrhea (–0.5; 95% CI, –0.908 to –0.125) and indigestion (–0.4; 95% CI, –0.747 to
–0.040) Gastrointestinal Symptoms Rating Scale (GSRS) domains. In addition, statistically significant mean improvements were seen in the same GSRS domains for patients with symptoms at baseline (Table 37).

Table 36: Patient-Reported Outcomes SF-36 and BPI-SF in ATTRACT and FACETS Trials (OLE Population Excluding Subjects With Non-Amenable Mutations)

	ATTRACT		FACETS	
	Migalastat-Migalastat N = 31	**ERT-Migalastat N = 15**	**Migalastat-Migalastat**	**PL-Migalastat**
SF-36v2, n				
Physical Component				
Actual: Baseline n Mean (SD)	 31 49.43 (9.762)	 15 40.53 (11.549)	-	-
Actual: OLE Month 30 n Mean (SD)	 31 50.25 (8.259)	 14 36.58 (12.193)	-	-
Change from Baseline to Month 30 n Mean (SD) 95% CI	 31 0.82 (8.316) (–2.23, 3.87)	 14 -3.25 (8.382) (–8.09, 1.59)	-	-
Mental Component				
Actual: Baseline n Mean (SD)	 31 50.37 (9.284)	 15 49.59 (10.089)	-	-
Actual: OLE Month 30 n Mean (SD)	 31 50.06 (11.847)	 14 48.90 (9.298)	-	-
Change from Baseline to Month 30 n Mean (SD) 95% CI	 31 –0.31 (11.372) (–4.48 to 3.86)	 14 0.07 (7.949) (–4.52 to 4.66)	-	-
BPI-SF (Pain Severity)				
Actual: Baseline n Mean (SD)	 31 1.68 (SD)	 15 2.87 (2.924)	-	-
Actual: OLE Month 30 n	 31	 14	-	-

	ATTRACT		FACETS	
	Migalastat-Migalastat N = 31	ERT-Migalastat N = 15	Migalastat-Migalastat	PL-Migalastat
Mean (SD)	2.48 (3.010)	2.86 (2.905)		
Change from Baseline to Month 30 n Mean (SD) 95% CI	 31 0.81 (2.701) (–0.18 to 1.80)	 14 0.0 (2.449) (–1.41 to 1.41)	-	-
Changes in the SF-36 After 18/24 Months of Migalastat Therapy (in Patients with Amenable Mutations)				
Vitality domain			4.0	
General health domain			4.5	

BPI = Brief Pain Inventory; CI = confidence interval; ERT = enzyme replacement therapy; OLE = open-label extension; PL = placebo; SD = standard deviation; SF-36v2 = Short-Form 36-Item Health Survey, version 2.
Sources: ATTRACT Clinical Study Report[19] and FACETS Clinical Study Report.[20]

Table 37: Mean Changes in GSRS in Stage 1 ITT Population and Open-Label Extension Population With Amenable Mutations of the FACETS Trial

GSRS Domain[a]	Diarrhea		Reflux		Indigestion	
Treatment Group	**Migalastat**	**Placebo**	**Migalastat**	**Placebo**	**Migalastat**	**Placebo**
Stage 1						
All patients, N	28	22	28	22	28	22
Mean Change From Baseline (Visit 1)						
All patients n Mean	 28 –0.3[b]	 19 0.2	 28 0.0	 19 0.2	 28 –0.1	 19 –0.1
Patients with symptoms at baseline n Mean	 17 -0.6	 10 0.2	 10 0.5[b]	 6 0.3	 23 –0.2	 18 –0.1
OLE						
All patients, N	42[c]		42[c]		42[c]	
Combined Mean Change From Baseline (Visit 1)						
All patients n Mean (95% CI)[d]	 40 –0.5 (–0.908 to –0.125)[e]		 40 –0.2 (–0.492 to 0.192)		 40 –0.4 (–0.747 to –0.040)[e]	
Patients with symptoms at baseline n Mean (95% CI)	 24 –1.0 (–1.519 to –0.424)[e]		 15 –0.6 (–1.480 to 0.213)		 36 –0.5 (–0.840 to –0.063)[e]	

CI = confidence interval; GSRS = Gastrointestinal Symptoms Rating Scale; ITT = intention-to-treat; OLE = open-label extension.
Note: Higher scores indicate greater severity of symptoms.
[a] Constipation and abdominal pain domains were not provided.
[b] *P* value < 0.05 from ANCOVA, comparing the difference in least-square means. The model includes treatment, baseline, and treatment by baseline interaction.
[c] Combine group.
[d] 95% CI is based on the mean.
[e] Statistically significantly different from baseline (visit 1) based on 95% CIs not overlapping with zero.
Source: FACETS Clinical Study Report.[20]

Safety

Detailed harms are presented in Table .

In the ATTRACT open-label extension (OLE), all 15 patients (100%) in the ERT-migalastat group and 50 patients (98%) in the migalastat-migalastat group experienced adverse events with the most common being nasopharyngitis (between 33% to 41%), headache (between 20% and 31%), influenza (between 20% to 24%), and diarrhea (between 22% to 27%). Sixteen patients (31%) in the migalastat-migalastat group and three (20%) patients in the ERT-migalastat group experienced serious adverse events and no deaths were reported in the OLE period.

In the FACETS trial, 24 (83%) and 24 (86%) of patients experienced at least one adverse event in the migalastat-migalastat and placebo-migalastat groups, respectively. The most common adverse events included nasopharyngitis, bronchitis, and proteinuria (Table). Serious adverse events were experienced by five (17%) and six (21%) patients in the migalastat-migalastat and placebo-migalastat group, respectively. In addition, there were no deaths reported.

Table 40: Harms Summary (Safety Population [ATTRACT] or OLE Population [FACETS])

	ATTRACT		FACETS[b]	
	All Migalastat During 0-30 Months N = 51	**ERT-Migalastat During 18-30 Months N = 15**	**Migalastat-Migalastat N = 29**	**PL-Migalastat N = 28**
AEs				
Patients with > 0 AEs, n (%)	50 (98)	15 (100)	24 (83)	24 (86)
Most common AE[a], n (%)				
Nasopharyngitis	21 (41)	5 (33)	-	-
Headache	16 (31)	3 (20)	3 (10)	3 (11)
Dizziness	8 (16)	2 (13)	-	-
Influenza	12 (24)	3 (20)	-	-
Abdominal pain	7 (14)	2 (13)	-	-
Diarrhea	11 (22)	4 (27)	-	-
Nausea	8 (16)	2 (13)	-	-
Back pain	5 (10)	-	-	-
Upper respiratory tract infection	5 (10)	1 (7)	-	-
Urinary tract infection	6 (12)	-	-	-
Cough	8 (16)	1 (7)	-	-
Vomiting	8 (16)	4 (27)	-	-
Sinusitis	-	0	-	-
Arthralgia	6 (12)	2 (13)	-	-
Bronchitis	5 (10)	2 (13)	-	-
Oedema peripheral	-	0	-	-
Gastritis	-	0	-	-
Pain in extremity	-	1 (7)	-	-
Dyspnea	-	1 (7)	-	-

	ATTRACT		FACETS[b]	
Procedural pain	-	0	-	-
Fatigue	-	2 (13)	-	-
Pyrexia	6 (12)	2 (13)	-	-
Blood creatine phosphokinase increased	7 (14)	2 (13)	-	-
Myalgia	6 (12)	-	-	-
Bronchitis	5 (10)	2 (13)	3 (10)	3 (11)
Insomnia	5 (10)	-	-	-
Pain	5 (10)	-	-	-
Palpitations	5 (10)	-	-	-
Tinnitus	5 (10)	-	-	-
Neuralgia	-	2 (13)	-	-
Diabetes mellitus	-	2 (13)	-	-
Muscle spasms	-	2 (13)	-	-
Poor quality sleep	-	2 (13)	-	-
Proteinuria	-	-	4 (14)	5 (18)
SAEs				
Subjects With > 0 SAEs, n (%)	16 (31)	3 (20)	5 (17)	6 (21)
Most Common SAEs, n (%)				-
Ventricular tachycardia	1 (2)	-	-	-
Hernia eventration	1 (2)	1 (7)	-	-
Chest pain	3 (6)	-	0	1 (4)[c]
Bile duct stone	1 (2)	-	-	-
Endocarditis	1 (2)	-	-	-
Perineal abscess	1 (2)	-	-	-
Pneumonia	1 (2)	-	-	-
Upper limb fracture	1 (2)	-	0	1(4)[d]
Obesity	2 (4)	-	-	-
Pheochromocytoma	1 (2)	-	-	-
Embolic stroke	1 (2)	-	-	-
Transient ischemic attack	1 (2)	1 (7)	1 (3)	0
Suicidal ideation	1 (2)	-	-	-
Proteinuria	1 (2)	-	-	-
Atelectasis	1 (2)	1 (7)	-	-
Dyspnea	1 (2)	1 (7)	-	-
Hemoptysis	1 (2)	-	-	-
Palpitations	-	-	1 (3)	0
Abdominal pain lower	-	-	0	1 (4)
Constipation	-	-	1 (3)	0
Fatigue	-	-	0	1 (4)
Malaise	-	-	1 (3)	0
Helicobacter gastritis	-	-	0	1 (4)
Paresthesia	-	-	0	1 (4)

	ATTRACT		FACETS[b]	
Syncope	-	-	0	1 (4)
Pheumothrorax	-	-	1 (3)	0
WDAEs, N (%)	0	0	0	0
Number of deaths, N (%)	0	0	0	0

AE = adverse event; ERT = enzyme replacement therapy; OLE = open-label population; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] AEs occurring in ≥ 10% of patients in the all migalastat group (safety population).
[b] Occurring in ≥ 10% of patients.
[c] Non-cardiac chest pain.
[d] Multiple fractures.
Source: ATTRACT Clinical Study Report.[19]

Critical Appraisal

The main limitations inherent to both the ATTRACT and FACETS extension studies were the open-label nature of this portion of the studies, the lack of a control group, and no inferential statistical testing. The aforementioned precludes the ability of one to ascertain either a statistical or clinical significance between the treatment and control groups.

Summary

There were no apparent differences in the efficacy outcomes associated with the open-label extension of either the ATTRACT or FACETS trials when compared with the main studies. In addition, there were no additional safety signals of concern that were associated with either the ATTRACT or FACETS trials. While there were no apparent differences in efficacy or safety, conclusions regarding the long-term efficacy and safety of migalastat in patients with Fabry disease are limited.

Appendix 7: Summary of GLA Mutational Assay

Objective

To summarize information regarding the mutations and the mutational assay that is used to assess whether patients with Fabry disease (FD) have amenable mutations to oral migalastat (chaperone therapy).

Findings

Alpha-Galactosidase A (GLA) Mutations

Mutations in the GLA gene encoding alpha-galactosidase A (alpha-Gal A) are responsible for the progressive X-linked disorder of Fabry disease (FD) and cause reductions in alpha-Gal A enzyme levels that subsequently enable accumulations of globotriaosylceramide (GL-3) in various cells throughout the body (which is thought to be associated with the life-threatening manifestations of FD).[18] More than 800 mutations have been identified to date,[17] with some causing completely undetectable levels of alpha-Gal A enzyme activity while others produce a wider variability in alpha-Gal A enzyme levels.[18] For the purposes of treatment with the chaperone therapy migalastat, GLA mutations are generally classified into types of mutations that are either “responsive” or amenable” and those that are “non-responsive” or “non-amenable” to treatment with migalastat.[17,18]

Amenable mutations are generally missense (whereby a single nucleotide change results in the coding for a different amino acid) or multiple-missense mutations and in-frame insertions or deletions. These types of mutations generally only affect a small number of amino acids and, for the most part, do not substantially affect the structure or function of alpha-Gal A protein.[18] This results in heterogeneous phenotypes, which can range in severity from non-classic to classic FD.[17] About 60% of the more than 800 identified mutations are missense mutations.[17] Non-amenable GLA mutations are responsible for one of three outcomes; they can significantly affect substrate binding or catalytic activity, they can cause impairments in alpha-Gal A enzyme synthesis, or they can significantly alter the length of the protein and significantly reduce enzyme levels or cause a complete loss of alpha-Gal A expression. Types of mutations responsible for producing non-amenable mutations include large insertions or deletions, nonsense mutations, or frameshifts, splice site, etc.).[17,18] While determining whether the mutations from males are amenable to migalastat is more precise (as they have only one copy of the affected gene on their only X chromosome), females pose a different problem in that their cells contain a mixture of mutant and wild-type forms of alpha-Gal A; both of which are responsive to migalastat.[17]

Good Laboratory Practice Human Embryonic Kidney 293 Cell In Vitro Assay

When developing the good laboratory practice (GLP) human embryonic kidney (HEK) assay, mutations causing FD that qualified for testing included missense and nonsense mutations near the carboxyl terminus, mutations where the reading frames were maintained (caused by small insertions or deletions), and mutations on a single allele that were considered complex because they were comprised of two or more of the aforementioned mutation types.[17] These qualifying mutations (of which there were 600) were identified from the Human Gene Mutations Database, clinical trials assessing migalastat, various public sources, and the Shire Human Genetic Therapies Fabry Outcome Survey registry.[17]

Another study by Benjamin et al.[17] used the validated GLP HEK in vitro assay to express 600 mostly missense mutations from FD patients to assess their response to migalastat. Amenable mutations were defined as a ≥ 1.20-fold-over-baseline increase or an absolute increase of ≥ 3.0% of the wild-type alpha-Gal A activity, when incubated in the presence of 10 umol/L migalastat.[17] To ascertain the clinical validation of the GLP HEK in vitro assay, mutant alpha-Gal A responses to migalastat in the GLP HEK assay were compared with pharmacodynamic effects of orally administered migalastat on the alpha-Gal A activity from peripheral blood mononuclear cells (PBMCs) isolated from male FD patients, mean GL-3 inclusions per kidney interstitial capillary in male FD patients, and globotriaosylsphingosine (lyso-Gb3) in both male and female FD patients. Of the 600 mutations, there was a statistically significant increase in alpha-Gal A activity from 360 mutant forms, of which approximately 45% (n = 268; the majority of which had missense mutations, with some patients having small in-frame insertions and deletions) met the criteria for having an amenable mutations.[17] The authors determined that there was a high degree of consistency between the assay results, PMBC alpha-Gal A activity, and disease substrate responses in FD patients treated with oral migalastat. In addition, they observed high sensitivity (0.92), specificity (0.89), and positive (0.9460; 95% CI, 0.8731 to 1.0188) and negative (1.0; 95% CI, 1.0 to 1.0) predictive values[47] that also provided evidence to support the clinical validity of the GLP HEK assay.[17]

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