NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Migalastat for treating Fabry disease [ID868]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - Amicus Therapeutics
   - MPS Society
   - Shire Pharmaceuticals

   Please note we received notification of no comments from the Department of Health

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Migalastat for treating Fabry disease

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
MPS Society	The MPS Society welcomes the evaluation committee's view to recommend Migalastat when used within its marketing authorisation, as a treatment option for Fabry patients aged 16 years and over with an amenable mutation. The clinical and patient views presented validated the clinical opinion that, Migalastat may not only be a comparable treatment to ERT but, may improve autonomy and quality of life for some patients due to it be an oral therapy. The MPS Society, supports the recommendations for further collection of both short and long term data for both Migalastat and ERT.	Many thanks for your comments. The benefits of oral administration are described in section 5.6 of the Final Evaluation Determination (FED).
Amicus Therapeutics	**Has all of the relevant evidence been taken into account?** We believe that all the relevant information has been taken into account. **Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** We have previously had the opportunity to express concerns over interpretation of the data by the ERG. In general we consider the interpretations to be reasonable. Some additional comments are provided below. <u>ECD</u> • Page 7 section 4.6 states: "The company stated that the prespecified criteria for comparability of migalastat and ERT in ATTRACT were met for both the co-primary outcomes of measured and estimated glomerular filtration rate. The results were considered confidential and cannot be reported here."	Many thanks for your comments. Section 4.6 of the FED has been amended to remove the reference to the confidentiality of this information. This section provides a succinct summary of the evidence, and detailed results for

Consultee	Comment	Response
	This is an inaccurate representation of the confidentiality data. The mITT results are not confidential and can be reported. Please replace with "The co-primary endpoints demonstrated that migalastat and ERT had comparable effects on renal function. The prespecified criteria for comparability of migalastat and ERT were met for both the $mGFR_{iohexol}$ and $eGFR_{CKD-EPI}$ outcomes: the annualised means were within 2.2 mL/min/1.73 m2/year and the 95% CIs for the means had greater than 50% overlap. That is, patients switched from ERT to migalastat met the prespecified criteria for comparability to patients who remained on ERT."	these outcomes are not included, for brevity.
	• Page 7 section 4.7 states: "There were no statistically significant differences in cardiac outcomes reported in the migalastat and ERT arms of ATTRACT" This is an inaccurate representation of the data. Please replace with "In ATTRACT at 18 months, patients switched from ERT to migalastat had significantly decreased LVMi from baseline ($p<0.05$), while LVMi was not significantly changed from baseline in patients remaining on ERT."	Section 4.7 of the FED clarifies that there was a significant decrease in LVMi in the migalastat group.
	• Page 14 states: "The committee was aware that the dose of agalsidase beta can be reduced when the condition is stable, although the effectiveness of this approach is not fully established and practice varies between centres." Lower doses of agalsidase beta are not licensed and this should be reflected in the final guidance.	Section 5.2 of the FED has been edited to state that reduced doses of agalsidase beta are not licensed.
	• Page 20 states: "The committee concluded that it is plausible that migalastat is associated with more health benefits than ERT as a result of its more convenient administration, but the ERG's estimates were more likely than the company's estimates." This appears to be an unfair difference in assumption between HST appraisals. In the appraisal of eliglustat, which took place on the same day, the ERG and HST committee appeared to prefer an assumed utility gain for oral treatments of 0.05 rather than the manufactures estimate of 0.12. Thus it appears that 0.05 was deemed reasonable for eliglustat and therefore acceptable for migalastat.	The committee considered that the utility gain associated with oral administration in this evaluation was highly uncertain. It heard from the ERG that the company's estimate lacked face validity, and considered that the ERG's estimates were more likely for this evaluation, although it did not specify that a particular utility value was 'correct'. Please see section 5.17 of the FED. The committee's considerations relating to eliglustat will be
	<u>Committee Papers - Pre-meeting briefing</u> • Page 21 states that there were imbalances in the baseline characteristics. We would like to point out that none of the imbalances in baseline characteristics in ATTRACT were	

Consultee	Comment	Response
	statistically significant. The ATTRACT study primary analysis was an ANCOVA that accounted for gender, baseline age, baseline GFR and baseline proteinuria. These are the parameters known to impact GFR and they were statistically accounted for. • Page 21 states: "However, due to the wide CIs for mGFR in the ATTRACT trial it is difficult to determine whether the change in mGFR in the OLE period represents improvement, stabilisation, or worsening of renal function." We feel that this statement is not a true reflection of the data. During the 12-month OLE of ATTRACT there was further stabilisation of GFR as measured by both eGFR and mGFR ($eGFR_{CKD-EPI}$ -1.72 ml/min/1.73m^2 [95% CI: -2.65, -0.78]; $mGFR_{iohexol}$ -2.75 ml/min/1.73m^2 [95% CI: 4.81, -0.68]). A comprehensive summary of studies in the literature assessing GFR in untreated and ERT-treated patients shows that annualised rates of decline in GFR are in the range of -2.2 to -12.7 ml/min/1.73m^2 in untreated patients and -2.2 to -2.9 ml/min/1.73m^2 in ERT-treated Fabry patients (Schiffmann et al., 2009; West et al., 2009; Branton et al., 2002; Schwarting et al., 2006). • Figure 2 on page 24 is incorrect. Although the figure as provided in the submission was incorrect we would request this to be updated to the correct schematic that was provided. **Are the provisional recommendations sound and a suitable basis for guidance on the use of migalastat in the context of national commissioning by NHS England?** Yes. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No.	outlined in the documents relating to that evaluation. Many thanks for the clarifications on the content of the pre-meeting briefing. These clarifications were considered by the committee at the second discussion. The pre-meeting briefing cannot be edited at this stage of the evaluation.

Consultee	Comment	Response
NHS England	1. NHS England is grateful for the opportunity to comment on the ECD. NHS England believes that not all of the relevant evidence has been taken into account. 2. The economic evaluation concluded that migalastat represents a cost-effective use of NHS resources when compared to enzyme replacement therapy (ERT). But the committee has not considered evidence whether enzyme replacement therapy for Fabry disease is itself a cost-effective use of NHS resources. 3. An evidence review published in 2006 estimated the cost per quality adjusted life year (QALY) of agalsidase beta (Connock et al Health Technology Assessment 2006; Vol. 10: No. 20). The central estimate was £252 000 but possibly over £600 000 in univariate sensitivity analysis. A more recent estimate from Hollak's group estimated the cost per QALY of ERT at over 5million Euro (Doi: 10.1016/j.ymgme.2011.11.141). A monograph which examined the experience of ERT as used currently in England concluded that the poor effectiveness of ERT meant that it was 'infeasible to conduct either a cost-effectiveness or a cost-utility analysis' (Wyatt et al Health Technology Assessment 2012; Vol. 16: No. 39.) 4. NHS England therefore believes that a Multiple Technology Assessment of all disease modifying therapies for Fabry disease is required before the committee can make a recommendation on migalastat.	Many thanks for your comments. The committee recognised that NICE has not evaluated enzyme replacement therapy (ERT) for Fabry disease. It considered that, given the scope for this evaluation and the established use of ERT in current clinical practice, its conclusions on the value for money of migalastat were appropriate. It further concluded that a complete evaluation of the costs and benefits of ERT for Fabry disease would be valuable. Please see section 5.21 of the FED.

The Department of Health stated that it had no comments on the evaluation consultation document.

Comments received from clinical specialists and patient experts

None

Comments received from commentators

Commentator	Comment	Response
Shire	**Shire consultation comments for NICE evaluation of Migalastat for treating Fabry disease**	Many thanks for your comments.

Commentator	Comment	Response
Pharmaceuticals	Shire would like to thank NICE for the opportunity to engage and comment on the draft advice for migalastat. It is our understanding that the Highly Specialised Evaluation Committee are interested in feedback on the following: • Has all of the relevant evidence been taken into account? • Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence? • Are the provisional recommendations sound and a suitable basis for guidance to NHS England? On the question of whether the summaries of clinical effectiveness are reasonable interpretations of the evidence, Shire has several areas of concern and would like to highlight points where we believe interpretation of the evidence is challenging based on the evidence supplied by the manufacturer and that which is currently available to the Fabry community. **Population** 1. Shire notes the Committee's consideration of how representative the ATTRACT study participants are to the Fabry population. We believe that the patient population that would benefit the most from migalastat needs to be clearer. The definition of amenable mutations needs to be clearly described to help the prescriber identify the appropriate patients. In addition, and in light of the requirement to ensure the patient has an amenable mutation, what safeguards should be put in place to ensure the correct tests are completed and the correct monitoring is in place prior to initiation of treatment? **Comparator (ERT)** 2. In section 5.2, the ECD states that "the committee understood that ERT may have a number of potential limitations including, limited penetration in key tissues……". Shire would like the Committee to address what impact, if any this has and what evidence, if any there is that migalastat can address it? We suggest that this be removed from the guidance. **Intervention (migalastat)/Amenability** 3. Shire has reservations on the issue of amenability in the ECD. We believe that there are considerable uncertainties that may lead to inappropriate treatment. These uncertainties include the following: a. Uncertainty around the ability to effectively and consistently identify amenable patients due to concerns around the assay including its reproducibility and potential variance in individual patient responses (Lukas et al., 2013, 2015). b. Uncertainty around the extent to which migalastat increases the delivery of enzyme to the relevant end organ tissues and the amount of enzyme that is required to produce a therapeutic effect.	The committee understood that migalastat is only suitable for people with an amenable mutation, based on a list compiled by the company as part of the marketing authorisation. Please see sections 3.1, 5.8 and 5.9 of the FED. Section 5.2 of the FED clarifies that the theoretical possibility of limited penetration of ERT into key tissues was based on clinical expert opinion. The list of amenable mutations is compiled and kept up to date by the company as part of the marketing authorisation for migalastat. The committee understood that its recommendations would apply only to people with amenable mutations. The committee also noted important uncertainties in the evidence presented for migalastat, and encouraged the company, NHS England and

Commentator	Comment	Response
	c. Any statements relating to comparability should at least relate to 'comparability in genetically amenable patients' to limit risk of inappropriate use. d. Likewise, any statements relating to starting criteria being 'the same' as for ERT ought to have the addition of 'for patients with amenable mutations'. 4. In section 5.8, the ECD states that "the company advised that there was variability in the in vitro response to migalastat according to mutation, but only mutations for which migalastat produced substantial increases in enzyme activity were judged amenable". Shire would like to see more evidence for clinicians as to why the criteria of amenability of 20% relative increase and 3% absolute increase in enzyme activity were considered clinically meaningful. Furthermore, given the questions that exist around the clinical relevance of these levels of enzyme activity it will be important to ensure a robust long-term follow-up programme is in place. **<u>Clinical trials</u>** 5. We note the Committee's consideration of the uncertainties in the clinical trials and wish to highlight several areas that we believe are important to consider when attempting to draw parallels of non-inferiority between migalastat and ERT. Firstly, we share the concerns stated by the ERG with regards to the pivotal phase III FACETS trial that looked into the proportion of patients with a ≥50% reduction from baseline to month six in the average numbers of GL-3 inclusions per kidney interstitial capillary. The results were not significantly different between migalastat and placebo and the categorical primary outcome may have overestimated response, i.e. due to small changes in patients with low baseline GL-3 inclusions. The EMA considered that GL-3 inclusions in renal tissue cannot be used to predict the clinical benefit of migalastat. 6. Furthermore, in the ATTRACT study there are a number of factors that hinder the conclusion of non-inferiority: a) *The statistical approach employed:* a standard non-inferiority analysis was not possible due to the small sample size so pre-specified criteria were used to define comparability. Shire has concerns with this approach and would like to highlight the small sample size and consequent questions relating to the power of the study in order to demonstrate non-inferiority. Additionally, we are concerned with the consideration of comparability where the lower bound of the 95 confidence interval exceeds the pre-specified non-inferiority margin. b) *The acceptable non-inferiority margins:* We would question how the non-inferiority margin was determined and the relevance of the value as an acceptable difference in the measured or estimated GFR (2.2mL/min/1.73m^2) over a period of 18 months. c) *The trial patient population:* The trial has a gender imbalance relative to the real-world Fabry population and this gender imbalance also raises questions around a conclusion of non-inferiority. *As a result of these issues Shire has concerns as to how non-inferiority has been assessed.*	treatment centres to collect more evidence. Please see sections 3.1 and 5.9 of the FED. The committee noted limitations and uncertainties in the evidence presented for migalastat, and encouraged the company, NHS England and treatment centres to collect more evidence. It noted that the trials had enrolled small populations, were short in relation to disease progression, and did not collect sufficient data to formally establish the clinical equivalence of migalastat and ERT. The committee concluded that, despite some important uncertainties, migalastat may provide similar outcomes to ERT. Please see sections 1.2 and 5.5 of the FED.

Commentator	Comment	Response
	Economic model 7. In section 4.20 of the ECD, the ERG noted that one of the limitations of the Markov model submitted by the manufacturer is the non-inclusion of different types of cardiac complications. However, in section 5.7, the ECD states that the committee heard from experts, that migalastat might be more beneficial in people with cardiac complications. It is Shire's position that the evidence to support this assertion is weak. **Adherence** 8. Shire notes the Committee's consideration of adherence and would like to point out that a 2 hour fast before and after taking migalastat is required. Given that the benefits can only be experienced if the adherence rates are high, Shire believes that a follow-up service to ensure that patients are adherent may be required. **Expert opinion** 9. Section 5.5 of the ECD states that the clinical experts gave their opinion that migalastat was at least as good as ERT. Shire would like to point out that based on the evidence that has been developed; it is not possible to state this. Thank you for your time and consideration.	The statement regarding migalastat's effect on cardiac complications was based on information provided by the clinical experts. Please see section 5.7 of the FED, Section 5.6 has been updated to include reference to the fasting period for migalastat. The committee was reassured that people with Fabry disease would be very motivated to continue treatment, and that the company was taking steps to support adherence. The committee considered the evidence on the clinical effectiveness of migalastat alongside information from the clinical experts. Please see section 5.5 of the FED.

Comments received from members of the public

None

Amicus Therapeutics

Response to Consultation on the Evaluation Consultation Document for Migalastat

Has all of the relevant evidence been taken into account?

We believe that all the relevant information has been taken into account.

Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?

We have previously had the opportunity to express concerns over interpretation of the data by the ERG. In general we consider the interpretations to be reasonable. Some additional comments are provided below.

<u>ECD</u>

- Page 7 section 4.6 states: "The company stated that the prespecified criteria for comparability of migalastat and ERT in ATTRACT were met for both the co-primary outcomes of measured and estimated glomerular filtration rate. The results were considered confidential and cannot be reported here."

This is an inaccurate representation of the confidentiality data. The mITT results are not confidential and can be reported. Please replace with "The co-primary endpoints demonstrated that migalastat and ERT had comparable effects on renal function. The prespecified criteria for comparability of migalastat and ERT were met for both the $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$ outcomes: the annualised means were within 2.2 mL/min/1.73 m^2/year and the 95% CIs for the means had greater than 50% overlap. That is, patients switched from ERT to migalastat met the prespecified criteria for comparability to patients who remained on ERT."

- Page 7 section 4.7 states: "There were no statistically significant differences in cardiac outcomes reported in the migalastat and ERT arms of ATTRACT"

This is an inaccurate representation of the data. Please replace with "In ATTRACT at 18 months, patients switched from ERT to migalastat had significantly decreased LVMi from baseline ($p<0.05$), while LVMi was not significantly changed from baseline in patients remaining on ERT."

- Page 14 states: "The committee was aware that the dose of agalsidase beta can be reduced when the condition is stable, although the

effectiveness of this approach is not fully established and practice varies between centres."

Lower doses of agalsidase beta are not licensed and this should be reflected in the final guidance.

- Page 20 states: "The committee concluded that it is plausible that migalastat is associated with more health benefits than ERT as a result of its more convenient administration, but the ERG's estimates were more likely than the company's estimates."

This appears to be an unfair difference in assumption between HST appraisals. In the appraisal of eliglustat, which took place on the same day, the ERG and HST committee appeared to prefer an assumed utility gain for oral treatments of 0.05 rather than the manufactures estimate of 0.12. Thus it appears that 0.05 was deemed reasonable for eliglustat and therefore acceptable for migalastat.

Committee Papers - Pre-meeting briefing

- Page 21 states that there were imbalances in the baseline characteristics.

We would like to point out that none of the imbalances in baseline characteristics in ATTRACT were statistically significant. The ATTRACT study primary analysis was an ANCOVA that accounted for gender, baseline age, baseline GFR and baseline proteinuria. These are the parameters known to impact GFR and they were statistically accounted for.

- Page 21 states: "However, due to the wide CIs for mGFR in the ATTRACT trial it is difficult to determine whether the change in mGFR in the OLE period represents improvement, stabilisation, or worsening of renal function."

We feel that this statement is not a true reflection of the data. During the 12-month OLE of ATTRACT there was further stabilisation of GFR as measured by both eGFR and mGFR ($eGFR_{CKD\text{-}EPI}$ -1.72 ml/min/1.73m^2 [95% CI: -2.65, -0.78]; $mGFR_{iohexol}$ -2.75 ml/min/1.73m^2 [95% CI: 4.81, -0.68]). A comprehensive summary of studies in the literature assessing GFR in untreated and ERT-treated patients shows that annualised rates of decline in GFR are in the range of -2.2 to -12.7 ml/min/1.73m^2 in untreated patients and -2.2 to -2.9 ml/min/1.73m^2 in ERT-treated Fabry patients (Schiffmann et al., 2009; West et al., 2009; Branton et al., 2002; Schwarting et al., 2006).

- Figure 2 on page 24 is incorrect.

Although the figure as provided in the submission was incorrect we would request this to be updated to the correct schematic that was provided.

Are the provisional recommendations sound and a suitable basis for guidance on the use of migalastat in the context of national commissioning by NHS England?

Yes.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

Response from the MPS Society to the ECD for Migalastat.
The MPS Society welcomes the evaluation committee's view to recommend Migalastat when used within its marketing authorisation, as a treatment option for Fabry patients aged 16 years and over with an amenable mutation.

The clinical and patient views presented validated the clinical opinion that, Migalastat may not only be a comparable treatment to ERT but, may improve autonomy and quality of life for some patients due to it be an oral therapy.

The MPS Society, supports the recommendations for further collection of both short and long term data for both Migalastat and ERT.

Kind regards

[redacted]

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08 November, 2016

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[redacted]

Shire consultation comments for NICE evaluation of Migalastat for treating Fabry disease

Shire would like to thank NICE for the opportunity to engage and comment on the draft advice for migalastat. It is our understanding that the Highly Specialised Evaluation Committee are interested in feedback on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to NHS England?

On the question of whether the summaries of clinical effectiveness are reasonable interpretations of the evidence, Shire has several areas of concern and would like to highlight points where we believe interpretation of the evidence is challenging based on the evidence supplied by the manufacturer and that which is currently available to the Fabry community.

Population

1. Shire notes the Committee's consideration of how representative the ATTRACT study participants are to the Fabry population. We believe that the patient population that would benefit the most from migalastat needs to be clearer. The definition of amenable mutations needs to be clearly described to help the prescriber identify the appropriate patients. In addition, and in light of the requirement to ensure the patient has an amenable mutation, what safeguards should be put in place to ensure the correct tests are completed and the correct monitoring is in place prior to initiation of treatment?

Comparator (ERT)

2. In section 5.2, the ECD states that "the committee understood that ERT may have a number of potential limitations including, limited penetration in key tissues……". Shire would like the Committee to address what impact, if any this has and what evidence, if any there is that migalastat can address it? We suggest that this be removed from the guidance.

Intervention (migalastat)/Amenability

3. Shire has reservations on the issue of amenability in the ECD. We believe that there are considerable uncertainties that may lead to inappropriate treatment. These uncertainties include the following:
    a. Uncertainty around the ability to effectively and consistently identify amenable patients due to concerns around the assay including its reproducibility and potential variance in individual patient responses (Lukas et al., 2013, 2015).
    b. Uncertainty around the extent to which migalastat increases the delivery of enzyme to the relevant end organ tissues and the amount of enzyme that is required to produce a therapeutic effect.
    c. Any statements relating to comparability should at least relate to 'comparability in genetically amenable patients' to limit risk of inappropriate use.

d. Likewise, any statements relating to starting criteria being 'the same' as for ERT ought to have the addition of 'for patients with amenable mutations'.

4. In section 5.8, the ECD states that "the company advised that there was variability in the in vitro response to migalastat according to mutation, but only mutations for which migalastat produced substantial increases in enzyme activity were judged amenable". Shire would like to see more evidence for clinicians as to why the criteria of amenability of 20% relative increase and 3% absolute increase in enzyme activity were considered clinically meaningful. Furthermore, given the questions that exist around the clinical relevance of these levels of enzyme activity it will be important to ensure a robust long-term follow-up programme is in place.

Clinical trials

5. We note the Committee's consideration of the uncertainties in the clinical trials and wish to highlight several areas that we believe are important to consider when attempting to draw parallels of non-inferiority between migalastat and ERT. Firstly, we share the concerns stated by the ERG with regards to the pivotal phase III FACETS trial that looked into the proportion of patients with a ≥50% reduction from baseline to month six in the average numbers of GL-3 inclusions per kidney interstitial capillary. The results were not significantly different between migalastat and placebo and the categorical primary outcome may have overestimated response, i.e. due to small changes in patients with low baseline GL-3 inclusions. The EMA considered that GL-3 inclusions in renal tissue cannot be used to predict the clinical benefit of migalastat.

6. Furthermore, in the ATTRACT study there are a number of factors that hinder the conclusion of non-inferiority:

   a) *The statistical approach employed:* a standard non-inferiority analysis was not possible due to the small sample size so pre-specified criteria were used to define comparability. Shire has concerns with this approach and would like

to highlight the small sample size and consequent questions relating to the power of the study in order to demonstrate non-inferiority. Additionally, we are concerned with the consideration of comparability where the lower bound of the 95 confidence interval exceeds the pre-specified non-inferiority margin.

b) *The acceptable non-inferiority margins:* We would question how the non-inferiority margin was determined and the relevance of the value as an acceptable difference in the measured or estimated GFR (2.2mL/min/1.73m^2) over a period of 18 months.

c) *The trial patient population:* The trial has a gender imbalance relative to the real-world Fabry population and this gender imbalance also raises questions around a conclusion of non-inferiority.

As a result of these issues Shire has concerns as to how non-inferiority has been assessed.

Economic model

7. In section 4.20 of the ECD, the ERG noted that one of the limitations of the Markov model submitted by the manufacturer is the non-inclusion of different types of cardiac complications. However, in section 5.7, the ECD states that the committee heard from experts, that migalastat might be more beneficial in people with cardiac complications. It is Shire's position that the evidence to support this assertion is weak.

Adherence

8. Shire notes the Committee's consideration of adherence and would like to point out that a 2 hour fast before and after taking migalastat is required. Given that the benefits can only be experienced if the adherence rates are high, Shire believes that a follow-up service to ensure that patients are adherent may be required.

Expert opinion

9. Section 5.5 of the ECD states that the clinical experts gave their opinion that migalastat was at least as good as ERT. Shire would like to point out that based on the evidence that has been developed; it is not possible to state this.

Thank you for your time and consideration.

Sincerely,

[redacted]