Migalastat hydrochloride (Amigal) for Fabry disease

December 2010

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Migalastat hydrochloride (Amigal) for Fabry disease

Target group
- Fabry disease: monotherapy – first line.

Background
Fabry disease (also known as Anderson-Fabry disease) is an inheritable, X-linked recessive disorder caused by insufficient activity of the lysosomal enzyme α-galactosidase A. The resulting inability to catabolise glycosphingolipids causes progressive accumulation of globotriaosylceramide in the cells of blood vessels and other organs such as the heart, kidney and brain. This results in a multi-systemic disorder characterised by renal, cardiac and cerebrovascular complications, failure of which are the major causes of morbidity. Patients also experience significant impact on their quality of life due to neuropathic pain and gastrointestinal symptoms. Unlike other X-linked disorders, signs and symptoms are experienced by females. These can be as severe as in males, though are usually milder and later in onset.

Technology description
Migalastat hydrochloride (Amigal, AT 1001) is a pharmacological chaperone. It is intended to bind to abnormal α-galactosidase A (α-Gal A) and recover native protein folding, allowing correct transportation to the lysosome and restoring protein activity. This would provide an alternative to enzyme replacement therapy (ERT) for the treatment of Fabry disease. In phase III clinical trials, migalastat hydrochloride is administered orally at 150mg once every other day.

Migalastat hydrochloride is in phase II development for the treatment of Fabry disease as a combination therapy with ERT.

Innovation and/or advantages
If licensed, migalastat hydrochloride would provide an alternative therapy for the treatment of patients with Fabry disease. Unlike existing ERTs, which are administered by intravenous (IV) infusion, migalastat hydrochloride is given orally, allowing therapy to be given at home and potentially reducing service costs.

Developer
Amicus Therapeutics Inc.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area
None identified.

Relevant guidance

Clinical need and burden of disease
Fabry disease is a rare pan-ethnic condition and is the second commonest of the 40 lysosomal storage disorders after Gaucher disease. Incidence figures vary, with a reported incidence of 1 in 117,000 in Australia and 1 in 476,000 in the Netherlands1. The EMA estimate EU prevalence of Fabry disease to be between 1 and 5 people per 100,000
population\(^2\), though two studies in the UK using a register of all known cases diagnosed between 1980 and 1995, reported prevalences of 0.27 cases per 100,000 population for males and 0.29 for females\(^3\). This equates to approximately 170 male and 180 female cases in England and Wales\(^4\), though the proportion of symptomatic females is unclear. In 2008, 1,133 finished consultant episodes\(^4\) and 19 deaths\(^5\) were reported in England and Wales with the diagnosis of sphingolipodosis (ICD10 E75.2, includes Fabry disease as well as other diseases).

**Existing comparators and treatments**

Fabry disease is currently incurable. However symptoms can be managed and now specific ERT allows better control of the disease. The UK guidelines for the diagnosis and management of Anderson-Fabry disease\(^1\) recommends the following treatment options:

**Enzyme replacement therapy (ERT):**

- Agalsidase alfa (Replagal) – human form of \(\alpha\)-Gal A produced through gene activation of a human fibroblast cell line.
- Agalsidase beta (Fabrazyme) – human form of \(\alpha\)-Gal A produced through recombinant DNA technology using mammalian Chinese hamster ovary (CHO) cell culture.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01218659, AT1001-012; migalastat hydrochloride vs agalsidase; phase III.</th>
<th>NCT00925301, AT1001-011; migalastat hydrochloride vs placebo; phase III.</th>
<th>NCT00526071, FAB-CL-205; migalastat hydrochloride; phase II extension.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Amicus Therapeutics.</td>
<td>Amicus Therapeutics.</td>
<td>Amicus Therapeutics.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^6).</td>
<td>Trial registry(^7) and manufacturer.</td>
<td>Trial registry(^8), manufacturer and abstract(^9).</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>EU (inc. UK), USA, Canada and other countries.</td>
<td>EU (inc. UK), USA, Australia and Brazil.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=60 (planned); adults 16 to 74 years; Fabry disease confirmed by GLA(^b) mutation; received ERT for at least 12 months. Randomised to migalastat hydrochloride given orally at 150mg once every other day alternating with placebo, or agalsidase IV given in accordance with product specification.</td>
<td>n=60 (planned); adults 16 to 74 years; Fabry disease confirmed by GLA mutation; never treated with ERT or not received ERT for 6 consecutive months. Randomised to migalastat hydrochloride at 150mg or placebo, both given orally once every other day.</td>
<td>n=27 (planned); adults 18 to 65 years; Fabry disease confirmed by GLA mutation; completed previous phase II trials of migalastat hydrochloride. Migalastat hydrochloride given orally at 150mg once every other day; or 250mg, 300mg or 500mg, all for 3 days followed by 4 days off.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Treatment period 18</td>
<td>2 month screening period</td>
<td>Treatment period 13</td>
</tr>
</tbody>
</table>

\(^a\) Based on the mid-2009 UK population estimate.  
\(^b\) GLA = \(\alpha\)- galactosidase gene.
<table>
<thead>
<tr>
<th>Months</th>
<th>Followed by 6 month treatment period</th>
<th>Months (assessment in clinic approximately every 3 months)</th>
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</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Renal function assessed by iohexol glomerular filtration rate.</td>
<td>Kidney globotriaosylceramide (GL-3) level.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Time to occurrence of events (renal, cardiac, cerebrovascular and/or death) cardiac function, pain, quality of life.</td>
<td>Urine GL3 level, renal function, safety, tolerability.</td>
</tr>
<tr>
<td>Key results</td>
<td>Preliminary results expected mid-2011.</td>
<td>Interim results (n=23); all patients who entered extension study maintained renal function for up to 3 years.</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>-</td>
<td>-</td>
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</table>

**Trial and Design**

**Trial**
- NCT00214500, FAB-CL-201; migalastat hydrochloride; phase II.
- FAB-CL-202, NCT00283959; migalastat hydrochloride; phase II.
- FAB-CL-203, NCT00283933; migalastat hydrochloride; phase II.
- FAB-CL-204, NCT00304512; migalastat hydrochloride; phase II.

**Sponsor**
- Amicus Therapeutics.
- Amicus Therapeutics.
- Amicus Therapeutics.

**Status**
- Complete but unpublished.
- Complete but unpublished.
- Complete but unpublished.

**Source of information**
- Trial registry10, manufacturer and poster11.
- Trial registry12, manufacturer and poster11.
- Trial registry13, manufacturer and poster11.

**Location**
- USA.

**Participants and schedule**
- n=9; adults 18 to 55 years; Fabry disease confirmed by GLA mutation; never treated with ERT or stable without ERT for at least 18 weeks.
- Migalastat hydrochloride given orally at 25mg, 100mg or 250mg twice daily, or 50mg once every other day.

**Follow-up**
- 28 day screening period followed by 12 weeks treatment period.

**Adverse effects (AEs)**
- Interim results; most common AEs reported were headache, arthralgia and diarrhoea.

**Key results**

Cumulative results for phase II trials FAB-CL-201, -202, -203 and -204:
No serious adverse events reported. All drug-related AEs mild to moderate and did not require intervention. Treatment with migalastat hydrochloride increased activity of α-Gal A, and reduced urinary GL-3 in the majority of responders.

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*Results provided by manufacturer.*
<table>
<thead>
<tr>
<th>Location</th>
<th>Australia and Brazil.</th>
<th>UK, Canada and France.</th>
<th>EU (inc UK), USA, Canada, Australia and Brazil.</th>
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<tbody>
<tr>
<td>Participants and schedule</td>
<td>n=4; adults 18 to 65 years; Fabry disease confirmed by GLA mutation; never treated with ERT or stable without ERT for at least 18 weeks. Migalastat hydrochloride given orally at 150mg once every other day.</td>
<td>n=5; adults 18 to 65 years; Fabry disease confirmed by GLA mutation; never treated with ERT or stable without ERT for at least 30 weeks. Migalastat hydrochloride given orally at 150mg once every other day.</td>
<td>n=9; female adults 18 to 65 years; Fabry disease confirmed by GLA mutation; never treated with ERT or stable without ERT for at least 18 weeks. Migalastat hydrochloride given orally at 50mg, 150mg or 250mg once every other day.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Treatment period 12 weeks (assessment in clinic every 4 weeks).</td>
<td>Treatment period 24 weeks (assessment in clinic every 4 weeks).</td>
<td>4 week screening period followed by 12 week treatment period, with possible 36-week extension. Follow-up 2 weeks.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Safety and tolerability.</td>
<td>Safety and tolerability.</td>
<td>Safety and tolerability.</td>
</tr>
<tr>
<td>Key results</td>
<td>See cumulative results of Phase II trials reported under FAB-CL-201.</td>
<td>See cumulative results of Phase II trials reported under FAB-CL-201.</td>
<td>See cumulative results of Phase II trials reported under FAB-CL-201.</td>
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**Estimated cost and cost impact**

The cost of migalastat hydrochloride is not yet known. The cost of comparator drugs are summarised in the table below\(^\text{15}\).

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Period: every 2 weeks</th>
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<tbody>
<tr>
<td>Replagal (agalsidase alpha)</td>
<td>0.2mg/kg body weight given every 2 weeks(^\text{d})</td>
<td>£4,988</td>
</tr>
<tr>
<td>Fabrazyme (agalsidase beta)</td>
<td>1mg/kg body weight given every 2 weeks.</td>
<td>£5,023.</td>
</tr>
</tbody>
</table>

**Claimed or potential impact – speculative**

**Patients**
- ☑ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or improved quality of life for patients and/or carers
- ☑ Quicker, earlier or more accurate diagnosis or identification of disease
- ☑ None identified
- ☐ Other:

**Services**
- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use: oral administration requires fewer clinic visits for therapy. 
- ☐ Other:
- ☐ None identified

\(^\text{d}\) Average adult body weight 76.9kg based on figures from Health Survey for England 2008.
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Costs

☐ Increased unit cost compared to alternative
☐ Increased costs: more patients coming for treatment
☐ Increased costs: capital investment needed
☐ New costs:
☐ Savings: reduced need for outpatient IV therapy.
☐ Other: uncertain unit cost compared to alternative therapy.

Other issues

☐ Clinical uncertainty or other research question identified:
Clinical relevance of reduced potential for antibody formation and increased tissue penetration not yet fully understood.
☐ None identified

References

9 Waldek S, Castelli J, Bragat A et al. Preliminary long-term safety, tolerability and assessments of renal function of adult Fabry patients receiving treatment with AT1001, a pharmacological chaperone, for up to 3 years, abstract. American College of Medical Genetics annual clinical genetics meeting. 2010. 276. Poster.