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# HEALTH TECHNOLOGY BRIEFING
# OCTOBER 2019

# Migalastat for Fabry disease in children aged 12 to 15 years

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| **NIHRIO ID** | 24194 | **NICE ID** | 10134 |
| **Developer/Company** | Amicus Therapeutics UK Ltd | **UKPS ID** | 654113 |

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| **Licensing and market availability plans** | Currently in phase III clinical trial. |

## SUMMARY


Migalastat is in clinical development for the treatment of Fabry disease for children aged 12 to 15 years old. Fabry disease is a rare genetic disorder caused by a defective gene (the GLA gene) in the body. In most cases, the defect in the gene causes a deficient quantity of the enzyme alpha-galactosidase A. This enzyme is necessary for the daily breakdown (metabolism) of a lipid (fatty substance) in the body called globotriaosylceramide abbreviated GL-3. When the proper metabolism of this lipids does not occur, GL-3 accumulates and leads to cell damage. The cell damage causes a wide range of symptoms including potentially life-threatening consequences such as kidney failure, heart attacks and strokes often at a relatively early age.

Migalastat works by stabilizing the body's own dysfunctional enzyme, so it can clear the accumulated disease substrate in patients who have amenable mutations. Migalastat is currently licenced for patients aged 16 or over with Fabry disease and an amenable mutation. If the license is extended, migalastat may offer an additional treatment option for paediatric subjects 12 to 15 years old with Fabry disease and an amenable mutation, who weight over 45Kgs.

# PROPOSED INDICATION

Proposed licence extension: Treatment for Fabry disease and amenable GLA variant in children aged 12 to 15 years weighing more than 45Kg.[1,2,a]

# TECHNOLOGY

## DESCRIPTION

Migalastat (Galafold, AT1001) is a low molecular weight iminosugar analogue of the terminal galactose residue on globotriaosylceramide (GL-3), which binds selectively and reversibly to the active sites of amenable mutant forms of α-galactosidase A enzyme.[3] Certain GLA mutations can result in the production of abnormally folded and unstable mutant forms of α-galactosidase A.[4] The binding to α-galactosidase A mutant form allows migalastat to act as a pharmacological chaperone, thereby stabilising migalastat-amenable mutant forms of α-galactosidase A in the endoplasmic reticulum and facilitating proper trafficking to lysosomes. Once in lysosomes, migalastat dissociates from α-galactosidase A as a result of the more acidic pH and higher concentration of substrates, allowing the enzyme to break down GL-3. Following dissociation from the enzyme, migalastat is rapidly removed from the cell and excreted.[3]

Migalastat is currently in clinical development for the treatment of Fabry disease and amendable GLA variant in paediatric subjects 12 to 15 years old. In the phase III clinical trial (NCT03500094), patients will receive one migalastat 123 mg capsule equivalent to 150 mg migalastat hydrochloride (HCl), every other day for 12 months.[1]

## INNOVATION AND/OR ADVANTAGES

The current therapeutic options for Fabry disease include enzyme replacement therapy (ERT) with intravenous (IV) agalsidase beta (approved globally) or agalsidase alpha (approved in the EU and elsewhere but not USA) and migalastat for patients with amenable gene mutations, along with supportive care to manage symptoms. The two ERTs are similar, but not identical, formulations of recombinant α-galactosidase A, and both provide clinical benefits in patients with Fabry disease. However, ERT is limited by several factors, including considerable clinical variation, high costs, a frequent incidence of mild to moderate infusion-related reactions (which may arise from immunoglobulin antibody formation specific to the infused enzyme), a lack of consensus with regards to the optimal age to initiate therapy and a life-long burden of biweekly IV infusions (i.e. every two weeks).[3]

A novel approach to overcome some of the limitations of ERT is pharmacological chaperone therapy using oral small molecule agents, which restores endogenous enzyme activity and degradation of GL3 and other disease substrates. Migalastat is an effective oral alternative which overcomes some of the limitations of ERT.[3]

Migalastat is the only treatment recommended by NICE as an option for treating Fabry disease in people over 16 years of age with an amenable mutation.[5]

The innovation this product brings is the licence extension of the age group to children aged 12-15 years with Fabry disease who weigh more than 45Kgs. The availability of an oral option in amenable children aged 12-15 may provide a benefit in avoiding lifelong infusions.[a]

[a] Information provided by Amicus Therapeutics

It is anticipated that the licence extension into patients aged 12 years and over will be based on a phase IIIb open-label, uncontrolled study that will evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of migalastat treatment in up to 20 paediatric patients aged 12 to <18 years of age and weighing ≥ 45 kg (NCT03500094).[1] This will provide the data required for the regulator to conclude that the migalastat treatment exposure-response relationship in patients aged 12 years and overweighing ≥ 45 kg is comparable with that in patients aged 16 years and over. This will then allow for extrapolation of the migalastat efficacy and safety data from patients aged 16 years and over into this extended patient population.[b]

This will not provide a new clinical data package for migalastat; however, this is to be expected when extending a licensed indication into a small patient subset of an ultra-orphan disease. It should be noted that the NHS England policy Commissioning Medicines for Children in Specialised Services (NHS England: 170001/P) issued in March 2017 concludes that this approach to extrapolation of efficacy data to paediatric patients from adequate studies in adults is sufficient to support the routine commissioning for children those medicines approved in adults by NICE /NHS England.[6] Therefore, although limited, the collective evidence on which the licence extension into patients aged 12 years and over will be based is clinically appropriate for commissioning purposes.[b]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Migalastat is already licenced in the EU/UK for patients aged 16 year old and over with Fabry's disease in the EU/UK.[7,8]
Common or very common side-effects include constipation; defaecation urgency; depression; diarrhoea; dizziness; dry mouth; dyspnoea; epistaxis; fatigue; gastrointestinal discomfort; headache; muscle complaints; nausea; pain in extremity; palpitations; proteinuria; sensation abnormal; skin reactions; torticollis; vertigo.[7]

Migalastat has the following regulatory designations:[9,10]

- An orphan drug in the EU in May 2006 for treatment of Fabry disease
- US FDA fast track designation in 2017 for Fabry disease.

# PATIENT GROUP

## DISEASE BACKGROUND

Fabry disease is a rare inherited lysosomal disease. In Fabry disease, an enzyme (A-galactosidase) responsible for the breakdown of waste products in the cells is deficient or absent. This leads to an accumulation of waste biological molecules (called globotriaosylceramide or Gb3) in various types of cell in many organs of the body. Fabry disease is an X-linked genetic disorder, therefore women with the disease will have one unaffected X chromosome and one affected X chromosome and can pass either of them onto their children. In men with the disease, their only X chromosome is affected. In this way they will always pass the affected chromosome to a daughter but will never pass it to a son. If one member of the family is affected by Fabry disease, it is possible that other relatives may also have the condition.[11]

Fabry disease is associated with a wide range of symptoms that usually worsen and change with age. In children, pain is often the most noticeable symptom together with spots on the skin (called angiokeratoma) and harmless changes to the eye (often referred to as corneal

[b] Information provided by Amicus Therapeutics

verticillata). In teenage years, spots may become more widespread, kidney impairment may be noted and fever associated with an inability to sweat and control body temperature may develop. Stomach and bowel problems may also develop (including diarrhoea, constipation and stomach cramps). In adult life, ringing in the ears (tinnitus), heart problems and stroke may occur. Kidney disease often progresses further. There are many variations in the severity and symptoms between individuals with Fabry disease.[11]

## CLINICAL NEED AND BURDEN OF DISEASE

According to the report performed by the Orphanet Report Series in January 2019, the birth prevalence estimated in Europe for Fabry disease was 0.22/100,000 people.[12] Applying the UK 2018 mid-year population estimate, this would equate to approximately 6 cases in England and Wales in children aged 12-15 years.[13]

The amenability rate is estimated to only be 35-50% of Fabry patients. Therefore, using the figures above would suggest that there are approximately 3 cases eligible for treatment in England and Wales (expert opinion).[c]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

Early diagnosis is important because some disease manifestations (Fabry cardiomyopathy) can be modified with enzyme replacement therapy. For the management of Fabry disease the following are recommended approaches: general support and advice such as psychological support, avoidance of precipitating factors for pain and tiredness, avoiding smoking, low-fat diet, low-sodium and low-protein diet, and genetic counselling. Besides that, is recommended the use of ERT, drugs to prevent endocarditis, pain attacks and cerebrovascular disease, as well as drugs to manage the advance of the disease.[14]

## CURRENT TREATMENT OPTIONS

Currently, agalsidase alfa may be given to children aged 7 years and older, and agalsidase beta to children 8 years and over, for the treatment of Fabry disease.[15]

## PLACE OF TECHNOLOGY

If the licence is extended, migalastat will offer an additional treatment option for paediatric subjects 12 to 15 years old with Fabry disease.

# CLINICAL TRIAL INFORMATION

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| **Trial** | NCT03500094, AT1001-020, EudraCT 2017-000146-21; age 12 to 17 years; migalastat; phase III | NCT04049760, AT1001-036; age 12 to 17 years; migalastat; phase III extension |
| **Sponsor** | Amicus Therapeutics | Amicus Therapeutics |
| **Status** | Ongoing | Ongoing |
| **Source of Information** | Trial registry[1] | Trial registry[2] |

[c] Information provided by Amicus Therapeutics

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| **Location** | Spain, United Kingdom, United States | Spain, United States |
| **Design** | Single arm, open label, uncontrolled | Long-term, single arm, open label |
| **Participants** | N=20 (planned); aged 12 to 17 years old diagnosed with Fabry disease, confirmed GLA variant that has shown to be responsive to AT1001 in vivo, weighs at least 45 kg at screening, and subject has never been treated with ERT or has not received ERT for 14 days prior to screening. | N=20 (planned); aged 12 to 17 years diagnosed with Fabry disease and who completed study AT1001-020. |
| **Schedule** | Treatment will be in 2 stages. Subjects will receive migalastat 123 mg capsule equivalent to 150 mg migalastat HCl administered every other day for 12 months.<br><br>Stage 1 will be a treatment period of approximately 1 month (4 weeks); Stage 2 will be a treatment period of 11 months and a 30-day (untreated) safety follow-up period. There will be no break in treatment between Stages 1 and 2. Prior to Stage 1, there will be a screening period lasting at least 14 days and up to 30 days (or more, if GLA genotyping is required). Stage 1 and 2 together will consist of a 12-month treatment period, and a 30-day safety follow-up period, for a total of approximately 13 months. | One migalastat 123 mg capsule equivalent to 150 mg migalastat HCl will be administered every other day during the treatment period. |
| **Follow-up** | 12 months | Baseline over time; Up to 5 years |
| **Primary Outcomes** | • Incidence of treatment emergent adverse event (TEAE), serious adverse event (SAE), and adverse event (AE) leading to discontinuation of study drug [Time frame: Month 12]<br>• Changes in clinical laboratory test results [Time frame: baseline over time; up to 12 months]<br>• Changes in vital signs [Time frame: baseline over time; up to 12 months]<br>• Changes in physical examination findings [Time frame: baseline over time; up to 12 months] | • Incidence of TEAEs, SAEs, and AEs leading to discontinuation of study drug [Time frame: month 60]<br>• Change in body weight in kilograms [Time frame: baseline over time; up to 5 years]<br>• Change in height in centimetres [Time frame: baseline over time; up to 5 years]<br>• Changes in ECG results [Time frame: baseline over time; up to 5 years]<br>• Incidence of changes in echocardiogram results [Time frame: baseline over time; up to 5 years] |

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| | • Change in body weight and height [Time frame: baseline over time; up to 12 months]<br>• Changes in Electrocardiogram (ECG) results [Time frame: baseline over time; up to 12 months]<br>• Changes in echocardiogram parameters [Time frame: baseline to Month 12/ET]<br>• Change in Tanner stage [Time frame: baseline to Month 12/ET]<br>• Use of concomitant medications [Time frame: baseline to Month 12/ET]<br>• Population pharmacokinetics (popPK) model that describes the relationship between weight and age and migalastat pharmacokinetics in paediatric subjects [Time frame: baseline to month 12/ET]<br>• PopPK: Maximum serum concentration (Cmax) [Time frame: Day 15-30, months 6 and 12/ET]<br>• PopPK: Minimum serum concentration (Cmin) [Time frame: Day 15-30, months 6 and 12/ET]<br>• PopPK: Time taken to reach the maximum concentration (tmax) [Time frame: Day 15-30, months 6 and 12/ET]<br>• PopPK: AUC0-T [Time frame: Day 15-30, months 6 and 12/ET]<br>• PopPK: Time taken for Cmax to drop in half (t½) [Time Frame: Day 15-30, months 6 and 12/ET]<br>• PopPK: CLss/F [Time frame: Day 15-30, months 6 and 12/ET]<br>• PopPK: Vss/F concentration [Time frame: Day 15-30, Months 6 and 12/ET] | • Change in Tanner stage [Time frame: every 6 months; up to 5 years]<br>• Incidence of concomitant medications use [Time frame: every 1 month; up to 5 years] |
| **Secondary Outcomes** | • Change in plasma levels of lyso-Gb3 [Time frame: baseline to months 3, 6, and 12/ET] | • Change in plasma levels of lyso-Gb3 [Time frame: every 6 months; up to 5 years] |

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| | • Change in eGFR [Time frame: baseline to months 1, 3, 6, and 12/ET]<br>• Change in urine protein and albumin levels [Time frame: baseline to months 3, 6, and 12/ET]<br>• Change in LVMi and other echocardiogram parameters [Time frame: baseline to month 12/ET]<br>• Change in gastrointestinal signs and symptoms and pain, as measured by e-diary responses (FABPRO-GI and Pain Questionnaire for Clinical Trials [24-hour version]) [Time frame: baseline to month 12/ET]<br>• Mean Patient Global Impression of Change (PGI-C) values [Time Frame: Months 3, 6 and 12/ET]<br>• Change in FPHPQ scores [Time frame: baseline to month 12/ET]<br>• Change in PedsQL scores [Time frame: baseline to month 12/ET] | • Change in eGFR [Time frame: every 6 months; up to 5 years]<br>• Change in urine protein [Time frame: every 6 months; up to 5 years]<br>• Change in albumin levels [Time frame: every 6 months; up to 5 years]<br>• Change in Left Ventricular Mass Index (LVMi) [Time frame: every year; up to 5 years]<br>• Change in Fabry-Specific Pediatric Health and Pain Questionnaire (FPHPQ) scores [Time frame: every 3; up to 5 years]<br>• Change in Pediatric and Quality of Life Inventory™ (PedsQL™) scores [Time frame: every 3 months; up to 5 years] |
| **Key Results** | - | - |
| **Adverse effects (AEs)** | - | - |
| **Expected reporting date** | Estimated primary completion date reported as September 2020. | Estimated primary completion date reported as June 2022. |

# ESTIMATED COST

Migalastat is already marketed in the UK. The NHS indicative price for a pack of 14 x 123mg migalastat capsule is £16153.85.[7]

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE Highly specialised technologies guidance. Migalastat for treating Fabry disease (HST4). February 2017.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Lysosomal Storage Disorders Service (Children). E06/S(HSS)/c.

- NHS England. NHS Highly Specialised Services Highlight Report 2016/17. February 2018.
- NHS England. Commissioning Medicines for Children in Specialised Services. Reference: NHS England: 170001/P. 2017.
- NHS Standard Operating Procedure for the treatment of Fabry Disease 2013 and 2019.

## OTHER GUIDANCE

- European Fabry Working Group. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. 2015.[16]

# ADDITIONAL INFORMATION

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