Integrating treatment advances for alpha-mannosidosis into effective MDT care

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by USF Health and touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by USF Health or touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in USF Health and touchIME activities*
- *USF Health and touchIME accepts no responsibility for errors or omissions*

Expert panel

Dr Barbara Burton

Northwestern University
Feinberg School of Medicine
Chicago, IL, USA

Dr Can Ficicioglu

Children's Hospital of Philadelphia
Philadelphia, PA, USA

Dr Christina Lampe

University of Giessen
Giessen, Germany

touch™ ENDOCRINOLOGY

Agenda

- Treatment needs along the lifespan of people living with alpha-mannosidosis
- Evolving treatment landscape targeting the pathophysiology of alpha-mannosidosis
- Integrating treatment advances into MDT management to optimize patient outcomes

MDT, multidisciplinary team.

Treatment needs along the lifespan of people living with alpha-mannosidosis

Dr Barbara Burton

Northwestern University
Feinberg School of Medicine
Chicago, IL, USA

touch™ ENDOCRINOLOGY

Clinical Subtypes of alpha-mannosidosis: Type 3

- **Immediately recognized** due to skeletal abnormalities
- Other key manifestations include
  - Progressive CNS involvement
  - Hepatomegaly
  - Myopathy
  - Coarse facial features
  - Developmental delay
- Obvious progression, early death

AM, alpha-mannosidosis; CNS, central nervous system

1. Köse E, et al. *Eur J Med Genet.* 2024;68:104927; 2. Ficicioglu C, Stepien KM. In: Adam MP, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 1993–2025; 3. Santoro L, et al. *Mol Genet Metab.* 2024;142:108444.

Clinical Subtypes of alpha-mannosidosis: Type 2

- **Clinically recognized ≤10 years of age**
- Key manifestations include
  - Skeletal abnormalities
  - Myopathy
  - Hearing loss
  - Speech delay
  - Recurrent infections
  - Developmental delay
- Slow progression

AM, alpha-mannosidosis; CNS, central nervous system

1. Köse E, et al. *Eur J Med Genet.* 2024;68:104927; 2. Ficicioglu C, Stepien KM. In: Adam MP, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 1993–2025; 3. Santoro L, et al. *Mol Genet Metab.* 2024;142:108444.

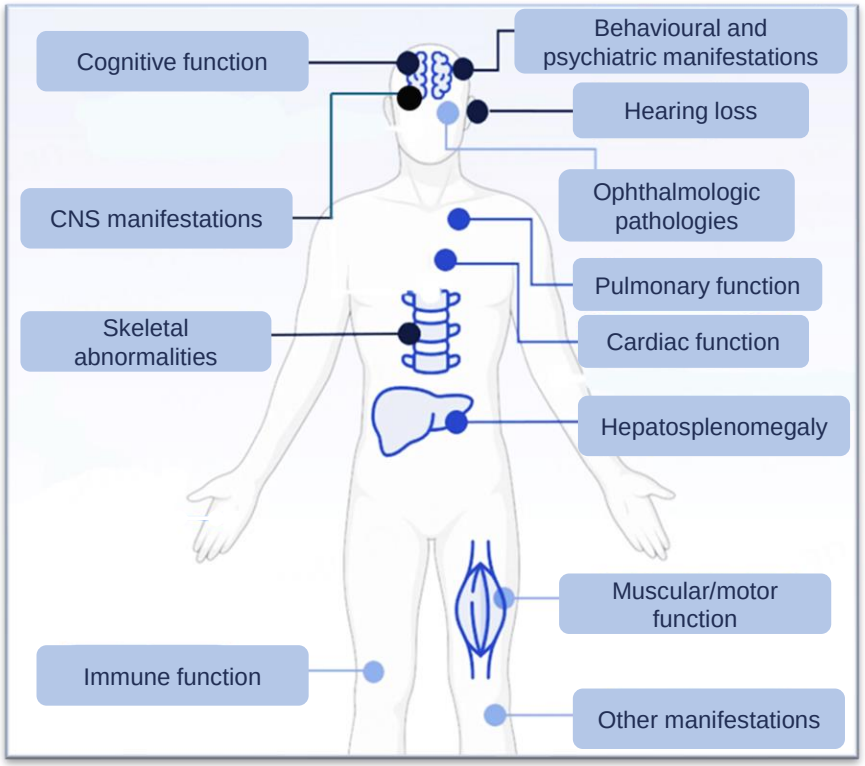
Clinical Subtypes of alpha-mannosidosis: Type 1

- **Clinically recognized >10 years of age**
- Key manifestations include
  - Hearing loss
  - Ataxia, muscular weakness
  - Psychiatric disorders
  - Cognitive impairment
- Slow progression

AM, alpha-mannosidosis; CNS, central nervous system

1. Köse E, et al. *Eur J Med Genet.* 2024;68:104927; 2. Ficicioglu C, Stepien KM. In: Adam MP, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 1993–2025; 3. Santoro L, et al. *Mol Genet Metab.* 2024;142:108444; 4. Guffon N, et al. *Mol Genet Metab.* 2019;126:470-474.

Non-specific multisystem manifestations hinder early diagnosis[1]



Initial signs and symptoms are not specific to the disease leading to diagnostic delays (mean delay ~5 years)[2]

1. Dewsbury MR, et al. *J Transl Genet Genom.* 2024;8:85–101; 2. Köse E, et al. *Eur J Med Genet.* 2024;68:104927.

touch™ ENDOCRINOLOGY

Evolving treatment landscape targeting the pathophysiology of alpha-mannosidosis

Dr Barbara Burton

Northwestern University
Feinberg School of Medicine
Chicago, IL, USA

touch™ ENDOCRINOLOGY

Disease-modifying treatments for alpha-mannosidosis: ERT

ERT[1,2]	Infusion of exogenous functional enzyme that does not cross the blood–brain barrier
Velmanase alfa	**EU indication:** Treatment of non-neurological manifestations in patients with mild-to-moderate AM[3] **US indication:** Treatment of non-CNS manifestations of AM in adult and paediatric patients[4]
Benefits	Phase III data show improvements in biochemical and functional parameters
Safety considerations	Administration may result in IRRs, incl. anaphylactoid reaction[3,4] IRRs may be mitigated by pre-treating with antihistamines, antipyretics, and/or corticosteroids[3,4]

AM, alpha-mannosidosis; CNS, central nervous system; ERT, enzyme replacement therapy; IRR, infusion-related reaction.

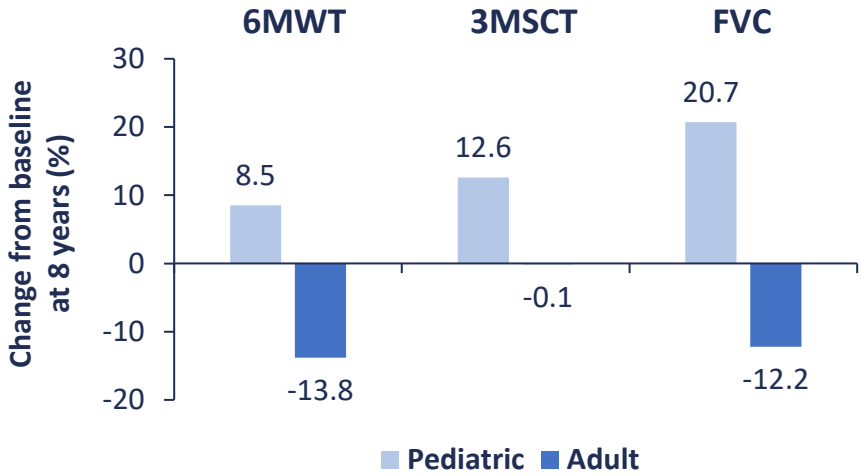
1. Diaz JCL, et al. *Int J Mol Sci.* 2022;1:232; 2. Ceccarini V, et al. *Int J Mol Sci.* 2018;19:1500; 3. EMA. Velmanase alfa SmPC. Available at: https://rb.gy/2bs8jd (accessed 26 March 2025); 4. FDA. Velmanase alfa PI. Available at: https://rb.gy/tznrwf (accessed 26 March 2025).

touch™ ENDOCRINOLOGY

Long-term efficacy with velmanase alfa: Up to 12 years

Pooled analysis from two phase IIIb extension trials rhLAMAN-07 (N=13) and rhLAMAN-09 (N=8)

Pooled analysis total N=21 (14 paediatric patients and 7 adults)



Additional efficacy endpoints

- sOLIGO clearance and sIgG level increase were sustained
- Hearing ability remained mostly stable

3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; FVC, forced vital capacity; sIgG, serum immunoglobulin G; sOLIGO, serum oligosaccharides.

Guffon N, et al. *J Inherit Metab Dis*. 2025;48:e12799.

Disease-modifying treatments for alpha-mannosidosis: HSCT

HSCT[1,2] — **Transplant functional enzyme-producing cells, with healthy donor cell CNS engraftment in patients with AM**

Benefits	Data are limited, but studies show HSCT attenuates CNS disease and can alleviate neuropathology[1]
Safety considerations	Reports of GvHD and cases of re-transplantation due to graft failure[2] Recipients are at higher risk for autoimmune haemolytic anaemia and pulmonary complications[3]

AM, alpha-mannosidosis; CNS, central nervous system; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplant.

1. Naumchik BM, et al. *Cells.* 2020;9:1411; 2. Mynarek M, et al. *Bone Marrow Transplant*. 2012;47:352–9; 3. Ceccarini V, et al. *Int J Mol Sci.* 2018;19:1500.

Integrating treatment advances into MDT management to optimize patient outcomes

Dr Barbara Burton

Northwestern University
Feinberg School of Medicine
Chicago, IL, USA

touch™ ENDOCRINOLOGY

Recommendations on short- and long-term follow-up care and coordination of care for patients

2024 DELPHI Consensus Study on Monitoring and Integrated Care

Assessments in newly diagnosed patients	• Genetic testing	• Baseline assessments
Routine follow-up and care	• Behavioural/psychiatric • Biochemical assays • Cardiac function • CNS manifestation • Cognitive impairment • Hearing assessments	• Immune function • Muscular/motor function • Ophthalmologic pathologies • Patient-reported outcomes • Skeletal abnormalities • Other manifestations
Treatment-related follow-up and care	• ERT-related monitoring • Post-HSCT monitoring	• Supportive care monitoring • Integrated care coordination

CNS, central nervous system; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant.
Guffon M, et al. *Mol Genet Metab*. 2024;142:108519.

touch™ ENDOCRINOLOGY