Migalastat Amenable Assay

The GLP-validated migalastat amenability assay is used to individually express Fabry disease-associated GLA variants in human embryonic kidney (HEK) 293 cells and measure increases in mutant α-Gal A activity in response to 10 μM migalastat.

1 A GLA variant is classified as amenable if it shows an increase in α-Gal A activity ≥1.2-fold above baseline and an absolute increase of ≥3% of wild-type (WT) α-Gal A activity.

Clinical Assessments

This descriptive analysis includes 6 patients from the phase 3 clinical trials FACETS (n=1) and ATTRACT (n=5), whose GLA variants resulted in an increase of ≥3% to ≤6% of WT α-Gal A activity in the in vitro migalastat amenability assay but still met the amenable criterion (≥1.2-fold relative increase above baseline).

FACETS (NCT01925301) is a randomized, double-blind, placebo-controlled study in ERT-naïve patients.

ATTRACT (NCT01218659) is a randomized, open-label, ERT-experienced study in ERT-experienced patients.

Patients who completed FACETS or ATTRACT had the option to continue migalastat treatment in the open-label extension (OLE) study (AT1001-041) and then switch to migalastat.

The effects of long-term migalastat treatment in Fabry disease patients previously treated with enzyme replacement therapy who have migalastat-amenable variants with relatively low α-Gal A activity in the in vitro migalastat amenability assay.

The Effects of Long-Term Migalastat Treatment in Patients With Fabry Disease Who Have Migalastat-Amenable Variants With Relatively Low Alpha-Galactosidase A Response in the In Vitro Migalastat Amenable Assay
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INTRODUCTION

Fabry disease is a rare, X-linked lysosomal disorder caused by pathogenic variants in the GLA gene, leading to the deficiency of functional α-galactosidase A (α-Gal A) in lysosomes.

Progressive accumulation of α-Gal A substrates, including globotriaosylceramide (GL-3) and globoseries glycosphingolipide (Lyso-GL-3), in multiple organ systems can lead to impairment of the kidney, heart, and brain, as well as premature death.

More than 1000 Fabry disease-associated GLA variants have been identified, many of them leading to the production of unstable, yet catalytically competent enzyme that is degraded prior to reaching lysosomes.

Migalastat, a first-in-class, oral pharmacologic chaperone, was designed to treat Fabry disease in patients with migalastat-amenable GLA variants by reversibly binding to endogenous α-Gal A variants. This binding stabilizes α-Gal A, allowing effective pronephric delivery toward the lysosomes where it degrades disease substrates.

Amenable GLA variants are identified with the good laboratory practice (GLP)-validated, in vitro migalastat amenability assay.

The efficacy and safety of migalastat in enzyme replacement therapy (ERT)-naive and ERT-experienced patients with amenable GLA variants have been demonstrated in 2 pivotal, phase 3 clinical trials (FACETS and ATTRACT).

OBJECTIVE

To evaluate the long-term effects of migalastat on α-Gal A activity and clinical outcomes in patients whose GLA variants demonstrated relatively small increases in α-Gal A activity in response to migalastat but met the amenable criterion in the in vitro migalastat amenability assay.

METHODS

Migalastat Amenable Assay

The GLP-validated migalastat amenability assay is used to individually express Fabry disease-associated GLA variants in human embryonic kidney (HEK) 293 cells and measure increases in mutant α-Gal A activity in response to 10 μM migalastat.

A GLA variant is classified as amenable if it shows an increase in α-Gal A activity ≥1.2-fold above baseline and an absolute increase of ≥3% of wild-type (WT) α-Gal A activity.

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RESULTS

Baseline Characteristics

Overall ATTRACT population

Forty-nine patients with amenable GLA variants received 21 dose of migalastat in ATTRACT.

Thirty-four patients were randomly assigned to receive migalastat from month 13 to patients completed 18 months of randomized ERT and then switched to migalastat.

Upon completion of ATTRACT, 21 patients continued migalastat treatment in the AT1001-041 OLE study. Another 20 patients continued migalastat treatment in the AT1001-042 OLE study.

Overall, mean±SD migalastat treatment duration was 2.3±0.9 years (range, 0.1 to 3.9).

The Effects of Long-Term Migalastat Treatment in Patients With Fabry Disease Who Have Migalastat-Amenable Variants With Relatively Low Alpha-Galactosidase A Response in the In Vitro Migalastat Amenable Assay
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