Original Investigation

Effect of Oral Eliglustat on Splenomegaly in Patients With Gaucher Disease Type 1
The ENGAGE Randomized Clinical Trial

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IMPORTANCE Gaucher disease type 1 is characterized by hepatosplenomegaly, anemia, thrombocytopenia, and skeletal disease. A safe, effective oral therapy is needed.

OBJECTIVE To determine whether eliglustat, a novel oral substrate reduction therapy, safely reverses clinical manifestations in untreated adults with Gaucher disease type 1.

DESIGN, SETTING, AND PARTICIPANTS Phase 3, randomized, double-blind, placebo-controlled trial conducted at 18 sites in 12 countries from November 2009 to July 2012 among eligible patients with splenomegaly plus thrombocytopenia and/or anemia. Of 72 patients screened, 40 were enrolled.

INTERVENTIONS Patients were stratified by spleen volume and randomized 1:1 to receive eliglustat (50 or 100 mg twice daily; n = 20) or placebo (n = 20) for 9 months.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was percentage change in spleen volume in multiples of normal from baseline to 9 months; secondary efficacy end points were change in hemoglobin level and percentage changes in liver volume and platelet count.

RESULTS All patients had baseline splenomegaly and thrombocytopenia (mostly moderate or severe), most had mild or moderate hepatomegaly, and 20% had mild anemia. Least-square mean spleen volume decreased by 27.77% (95% CI, −32.57% to −22.97%) in the eliglustat group (from 13.89 to 10.17 multiples of normal) vs an increase of 2.26% (95% CI, −2.54% to 7.06%) in the placebo group (from 12.50 to 12.84 multiples of normal) for an absolute treatment difference of −30.03% (95% CI, −36.82% to −23.24%; $P < .001$). For the secondary end points, the least-square mean absolute differences between groups all favored eliglustat, with a 1.22-g/dL increase in hemoglobin level (95% CI, 0.57-1.88 g/dL; $P < .001$), 6.64% decrease in liver volume (95% CI, −11.37% to −1.91%; $P = .007$), and 41.06% increase in platelet count (95% CI, 23.95%-58.17%; $P < .001$). No serious adverse events occurred. One patient in the eliglustat group withdrew (non–treatment related); 39 of the 40 patients transitioned to an open-label extension study.

CONCLUSIONS AND RELEVANCE Among previously untreated adults with Gaucher disease type 1, treatment with eliglustat compared with placebo for 9 months resulted in significant improvements in spleen volume, hemoglobin level, liver volume, and platelet count. The clinical significance of these findings is uncertain, and more definitive conclusions about clinical efficacy and utility will require comparison with the standard treatment of enzyme replacement therapy as well as longer-term follow-up.

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