Zhan and colleagues\(^1\) describe hematologic, visceral, and chemical biomarker outcomes in 28 Chinese individuals (17 children and 11 adults) with Gaucher disease (GD) who were treated with ambroxol for a mean (SD) of 2.6 (1.7) years.\(^1\) Two children had early-onset neuronopathic disease (GD3) with genotypes p.L483P/L483P and L483P/D448H, and 1 child had intermediate disease (GD2-3) with genotype R202X/R535C. Among the 15 patients classified as having nonneuronopathic GD (GD1), 1 was homozygous for L483P and 7 had a single L483P allele. No individual had even a single neuroprotective N409S \(^{GBA1}\) variant, whose presence is confined to European-derived populations.

Seven of 11 patients who had anemia before starting ambroxol treatment achieved normal hemoglobin concentrations. Substantial decreases in hepatomegaly were observed in 6 of 8 evaluable patients. In patients treated for at least 2 years, plasma glucosylsphingosine and chitotriosidase concentrations decreased by 34.1% and 43.1%, respectively, from markedly elevated pretreatment levels. However, responses in thrombocytopenic and splenomegalic patients showed only small incremental increases in platelet count. Only 2 of 21 patients attained platelet counts greater than 120 cells \(\times 10^3/\mu L\). Platelet counts failed to improve or decreased in 9 patients. Spleen volumes decreased in 4 of 8 evaluable patients, but the spleen volume decreased to less than 8 multiples of normal in only 1 patient. The best responses were observed in younger patients with \(^{GBA1}\) genotypes known to be associated with milder GD manifestations. There were no major safety issues.

In most high-income countries, symptomatic patients with GD1 usually have recourse to several safe and effective treatments, either intravenous enzyme replenishment therapy (ERT) or oral substrate restriction therapy (SRT). However, ERT and SRT are both very expensive. Additionally, each treatment category is imperfect and associated with unmet therapeutic needs or potential adverse effects. ERT is limited by uneven tissue distribution, occasional infusion reactions, exclusion from the central nervous system by the blood brain barrier, and, sometimes, poor venous access. Eliglustat SRT is restricted by exclusions, including children, pregnant and breastfeeding women, patients with advanced cardiac or liver disease, and those using incompatible concurrent medications that are metabolized by cytochrome P450 2d6 or 3A. Miglustat, which is approved as a second-line agent, causes frequent and severe gastrointestinal adverse events and, possibly, peripheral neuropathy.\(^2\) Thus, there is an opportunity to develop new therapies.

Of the more than 500 known pathogenic \(^{GBA1}\) variant alleles, many, including those that are rarely encountered by Western geneticists, are transcribed and translated by endoplasmic reticulum (ER)-bound polyribosomes into misfolded variant glucocerebrosidase (GCase) protein. On translocation into the ER, the misfolded GCase is conformationally unable to undergo N-glycosylation and/or binding to endogenous chaperones, steps that are essential for trafficking to the Golgi and, thence, to the lysosome. Rather, the variant enzyme is ubiquitinated and designated for ER-associated degradation in the proteasome, a compensatory mechanism termed the unfolded protein response, which eventually is overwhelmed, resulting in ER retention and aggregation of the misfolded protein. This process converges with lysosomal dysfunction attributable to storage of poorly soluble glucosylceramide and secondary related substrates, aggregation of additional lysosome-processed proteins such as α-synuclein, leakage of cathepsins and other lysosomal hydrolases, disruption of the vital autophagy-lysosomal pathway, mitochondrial degradation (mitophagy) with progressive cellular energy deficits, plasma membrane instability, extrusion of
extracellular vesicles, cell death, and perpetuation of an overall inflammatory cascade expressed at the patient level in terms of morbidity and sometimes early mortality.³

Pharmacological chaperones are small molecules that help refold variant proteins and enzymes, thus rescuing posttranslational modifications, preventing ER-associated degradation and/or unfolded protein response, restoring normal trafficking, and delivering at least somewhat functional lysosomal enzyme sufficient to avert the downstream pathophysiology described above. For GD, although several potential GCase chaperone molecules have been identified by computational modeling studies over the last several years, only 1 molecule, isofagamine, an iminosugar competitive inhibitor that binds GCase in the ER and dissociates in the lysosome, has undergone clinical trial. Despite encouraging preclinical and human cell culture results showing enhanced intracellular enzyme activity, a trial⁴ of a small number of patients failed to show a meaningful clinical benefit. Migalastat for Fabry disease (α-galactosidase deficiency) is the only approved pharmacological chaperone for a lysosomal storage disease and is effective only for specific amenable variants.

Ambroxol has long been used as an over-the-counter drug in much of the world as a mucolytic agent for respiratory diseases. In 2009, Maegawa et al⁵ identified ambroxol as a mixed active and nonactive sites GCase inhibitor at neutral pH that enhanced variant GCase activity and protein levels in GD fibroblasts primarily in the lysosomal acidic milieu. As shown in human GD cell lines, ambroxol chaperone activity, like migalastat, is GBA1 variant dependent, enhancing GCase activity in cells with wild-type GBA1 and in those with N409S alleles. However, the effect of ambroxol was less predictable in cells with L483P variants, especially when associated with complex alleles or other genotypes, which collectively are those most prevalent in much of the world.⁶

On the basis of low evidentiary observational studies, high-dose oral ambroxol can decrease or reverse seizure activity in children with GD3. However, because ambroxol's effects also include inhibition of pH-neutral, nonlysosomal glucocerebrosidase (GBA2), sodium channel blockade, upregulation of intracellular antioxidant and antiapoptotic signaling pathways, and anti-inflammatory and immunomodulatory effects, it is uncertain to what extent reported improvements in neurological manifestations in children with GD3 are solely a function of lysosomal GCase activity enhancement.⁴

Regarding ambroxol and GD1, although the safety profile seems favorable, clinical responses reported by Zhan et al¹ and Istaiti et al,⁷ albeit in very different populations, appear less robust than those reported for ERTs and eliglustat. Perhaps a disconnect exists between the reported good neurological responses and the middling systemic responses, as hinted at in a recent case report⁸ in which an infant with type 2 GD who started ambroxol shortly after birth had no neurological progression after 4 years yet had rapid systemic progression requiring institution of ERT.

Even if the results of Zhan et al¹ and similar observational studies were more compelling, there are many valid outstanding scientific and clinical questions for which there are no shortcut answers. Can in vitro GCase assays using mixed cell homogenates and detergent activators reliably predict in vivo cellular and patient responses?⁹ Is knowledge of the GBA1 exome sufficient to predict patient response or are there substantial intronic and epigenetic variables to consider? Without pharmacokinetic data for ambroxol administered to patients with GD in different formulations (tablets, syrup, and caplets of different strengths), how can optimal dosing be determined? How does this affect patient adherence, which was problematic in the study by Istaiti et al⁷ and dose-limiting in the study by Zhan et al⁴?

Overall, there is no plan for randomized prospective studies to assess the efficacy of ambroxol in large, varied populations of patients with GD. Despite the potential for substantial societal cost savings should repurposed ambroxol prove effective as a GD treatment, there is little financial incentive for the pharmaceutical industry to invest in an off-patent product for a rare disease with a small potential market. Given this reality and the need to provide affordable care for patients with GD with aggressive phenotypes worldwide, studies such as that by Zhan et al¹ should be encouraged and bolstered through collaborative input from all researchers whose expertise can provide added value. For example, deployment, perhaps under the aegis of the International Gaucher Alliance, of single
or regional centers as a worldwide resource for total GBA1 genome sequencing even for known genotypes and computational modeling and classification of rare alleles for prognostication and potential for small molecule enhancement of GCase activity by ambroxol or any other repurposed drugs for trial use in patients lacking access to or in conjunction with to approved ERT and/or SRT would be helpful.