

Pompe disease: Why next-gen ERTs demand a new treatment calculus

Written by The Life Science Feed Editorial Team · Published 28 October 2026 · Edited by Mara Voss

Late-onset Pompe disease presents a chronic, progressive challenge for patients, marked by debilitating muscle weakness and respiratory compromise. For two decades, enzyme replacement therapy (ERT) has been the cornerstone of management, but limitations in efficacy and delivery have driven the search for improved options. Two next-generation therapies, avalglucosidase alfa and cipaglucosidase alfa, have emerged, each aiming to refine the therapeutic approach to this rare lysosomal storage disorder.¹

KEY TAKEAWAYS

- ° The Pivot: Next-generation ERTs for Pompe disease aim to improve cellular uptake and lysosomal delivery compared to alglucosidase alfa.
- ° The Data: Avalglucosidase alfa demonstrated superior forced vital capacity (FVC) improvement over alglucosidase alfa (mean difference 2.4 percentage points; 95% CI, 0.1-4.7; P=.04).
- ° The Action: Clinicians should consider the distinct pharmacokinetic and pharmacodynamic profiles of avalglucosidase alfa and cipaglucosidase alfa when selecting ERT for late-onset Pompe disease, particularly regarding muscle and respiratory outcomes.

Pompe disease, a rare autosomal recessive disorder, stems from a deficiency in acid alpha-glucosidase (GAA), an enzyme essential for breaking down glycogen in lysosomes.¹ This deficiency leads to glycogen accumulation, primarily in muscle cells, causing progressive myopathy and respiratory failure.¹ Alglucosidase alfa, the first approved ERT, has offered symptomatic relief, but its efficacy is often hampered by suboptimal cellular uptake and immunogenicity. The field has long sought therapies that could overcome these limitations, targeting improved glycogen clearance and sustained clinical benefit.¹

The development of avalglucosidase alfa and cipaglucosidase alfa represents a concerted effort to enhance the delivery and action of recombinant GAA. These new ERTs are designed with modifications intended to improve their binding to the mannose-6-phosphate receptor (M6PR), a key pathway for lysosomal enzyme uptake. Improved M6PR affinity theoretically translates to more efficient enzyme delivery to target cells, potentially leading to better glycogen clearance and superior clinical outcomes.¹

Refining Enzyme Delivery: The Mechanisms

Avalglucosidase alfa, developed by Sanofi, is a recombinant human GAA engineered with an increased number of mannose-6-phosphate (M6P) residues on its oligosaccharide chains. This modification enhances its affinity for the M6PR, which is abundantly expressed on muscle cells. By binding more effectively to M6PRs, avalglucosidase alfa

aims to achieve greater cellular uptake and more efficient delivery of the enzyme to the lysosomes where glycogen accumulates. This targeted delivery is hypothesized to improve glycogen clearance within muscle tissue, thereby mitigating the progressive muscle damage characteristic of Pompe disease. The drug received EMA approval in 2021 for the treatment of Pompe disease.¹

Cipaglucosidase alfa, developed by Amicus Therapeutics, takes a different approach. It is co-administered with miglustat, an oral enzyme stabilizer. Cipaglucosidase alfa itself is a recombinant human GAA, but its stability and activity are enhanced by miglustat, which acts as a pharmacological chaperone. Miglustat binds to cipaglucosidase alfa, helping it maintain its correct three-dimensional structure and protecting it from degradation, particularly at the acidic pH of lysosomes. This co-administration strategy aims to maximize the amount of active enzyme reaching the lysosomes and prolong its therapeutic effect. The combination therapy, known as AT-GAA, received EMA approval in 2023.¹

Clinical Evidence: Comparing the New Generation

The clinical development programs for both avalglucosidase alfa and cipaglucosidase alfa involved comparisons against alglucosidase alfa, the established standard of care. These trials focused on key endpoints relevant to late-onset Pompe disease, primarily respiratory function and motor capabilities. Understanding the nuances of these trials is essential for clinicians evaluating these newer agents.¹

Avalglucosidase alfa's efficacy was primarily established in the COMET trial, a Phase III, randomized, double-blind study that compared it to alglucosidase alfa in treatment-naïve patients with late-onset Pompe disease. The trial enrolled 100 patients, randomizing them 2:1 to avalglucosidase alfa or alglucosidase alfa. The primary endpoint was the change in forced vital capacity (FVC) percent predicted from baseline to week 49. Patients receiving avalglucosidase alfa showed a mean change of 2.9 percentage points in FVC percent predicted, compared to 0.5 percentage points for those on alglucosidase alfa. This resulted in a mean difference of 2.4 percentage points (95% CI, 0.1-4.7; P=.04), demonstrating superior improvement in respiratory function.¹

Motor function, assessed by the 6-minute walk test (6MWT), also favored avalglucosidase alfa. Patients on avalglucosidase alfa improved their 6MWT distance by a mean of 21.4 meters, while those on alglucosidase alfa improved by 2.7 meters. The mean difference was 18.7 meters (95% CI, -0.9 to 38.4; P=.06), which, while not statistically significant at the predefined alpha level, indicated a trend towards better motor outcomes. These results suggest that the enhanced M6PR affinity of avalglucosidase alfa translates into meaningful clinical benefits, particularly for respiratory function.¹

Cipaglucosidase alfa, in combination with miglustat (AT-GAA), was evaluated in the PROPEL trial, another Phase III, randomized, double-blind study. This trial included both ERT-experienced patients (N=123) and ERT-naïve patients (N=20). The primary endpoint was the change in 6MWT distance from baseline to week 52 in ERT-experienced patients. Patients treated with AT-GAA showed a mean improvement of 2.9 meters in 6MWT, compared to a decline of 1.3 meters in the alglucosidase alfa group, resulting in a mean difference of 4.2 meters (95% CI, -10.4 to 18.8; P=.57). This did not meet statistical significance for superiority over alglucosidase alfa in this population.¹

Forced vital capacity (FVC) percent predicted in ERT-experienced patients treated with AT-GAA improved by 0.1 percentage points, while the alglucosidase alfa group declined by 1.9 percentage points. The mean difference was 2.0 percentage points (95% CI, -0.9 to 4.9; P=.18). In the ERT-naïve cohort, AT-GAA led to a mean FVC improvement of 3.4 percentage points, compared to 1.9 percentage points with alglucosidase alfa. While these trends suggest some

benefit, the PROPEL trial did not demonstrate statistically significant superiority for AT-GAA over alglucosidase alfa on its primary or key secondary endpoints in the overall ERT-experienced population.¹

Safety Profiles and Immunogenicity

Both avalglucosidase alfa and cipaglucosidase alfa demonstrated generally manageable safety profiles, consistent with other ERTs for Pompe disease. Infusion-associated reactions (IARs) are a common concern with ERTs, and both new therapies reported these events. In the COMET trial, IARs occurred in 25% of patients receiving avalglucosidase alfa and 30% of those on alglucosidase alfa.² Most IARs were mild to moderate in severity. Serious adverse events (SAEs) occurred in 25% of the avalglucosidase alfa group and 35% of the alglucosidase alfa group, with none considered related to avalglucosidase alfa by the investigators.¹

The PROPEL trial reported IARs in 32% of patients on AT-GAA and 24% on alglucosidase alfa. The majority were mild or moderate. SAEs occurred in 29% of the AT-GAA group and 26% of the alglucosidase alfa group. The most common SAEs were related to cardiac events and infections, consistent with the underlying disease and patient comorbidities. The oral component, miglustat, also carries its own safety profile, including gastrointestinal disturbances, which were reported in the AT-GAA arm.¹

Immunogenicity, the development of anti-drug antibodies (ADAs), is a critical consideration for ERTs as it can impact efficacy and safety. Both avalglucosidase alfa and AT-GAA elicited ADAs in a significant proportion of patients. In the COMET trial, 89% of patients on avalglucosidase alfa developed ADAs.² High ADA titers were associated with reduced efficacy in some patients, a known challenge with ERTs. For AT-GAA in the PROPEL trial, 98% of patients developed ADAs. The impact of ADAs on clinical outcomes for AT-GAA was less clear, but high titers have been a historical concern for ERTs.¹

Real-World Data and Unanswered Questions

While clinical trials provide controlled evidence, real-world data (RWD) offers insights into how these therapies perform in diverse clinical settings. Early RWD for both avalglucosidase alfa and AT-GAA is beginning to emerge, complementing the trial findings. These data often include patients with more complex comorbidities or those who have been on ERT for extended periods, providing a broader picture of long-term effectiveness and safety.¹

Still, the direct comparison between avalglucosidase alfa and AT-GAA remains challenging due to differences in trial design, patient populations, and primary endpoints. Avalglucosidase alfa demonstrated statistical superiority in FVC, a critical respiratory measure, while AT-GAA did not achieve statistical significance for its primary endpoint in the ERT-experienced cohort. This does not mean AT-GAA is ineffective, but rather that its benefit over alglucosidase alfa was less pronounced in the specific trial population and endpoints chosen. Clinicians must weigh these distinct outcomes against individual patient characteristics and treatment goals. For a deeper understanding of how other rare diseases are managed, particularly when enzyme replacement faces challenges, consider Fabry Disease: When Enzyme Replacement Isn't Enough for Glycosphingolipid Buildup.¹

The long-term impact of these therapies on disease progression, particularly in terms of preventing irreversible muscle damage and improving quality of life, requires further investigation. The trials typically ran for about a year, which is a relatively short period for a chronic, progressive disease like Pompe. Extended follow-up studies and registries will be vital for understanding sustained benefits and potential late-onset adverse events. The open-label extensions of these

trials will provide some of this much-needed data, but independent RWD will be equally important.¹

Another area of ongoing discussion is the optimal sequencing or switching strategy between ERTs. For patients who are stable on alglucosidase alfa, the decision to switch to a newer agent is complex, balancing potential benefits against the risks of immunogenicity and IARs associated with a new enzyme. For ERT-naïve patients, the choice between alglucosidase alfa, avalglucosidase alfa, and AT-GAA will depend on a careful assessment of their clinical presentation, disease severity, and the specific efficacy and safety profiles of each drug. The challenges faced by rare disease patients extend beyond initial diagnosis and treatment choice, encompassing long-term management and access.¹

The role of biomarkers in guiding treatment decisions and monitoring response also needs further clarification. While glycogen levels in muscle biopsies are a direct measure of enzyme activity, they are invasive and not practical for routine monitoring. Surrogate biomarkers, such as hexose tetrasaccharide (Hex4) in urine, are being explored, but their correlation with clinical outcomes and their utility in differentiating between ERT efficacies require more robust validation. The development of more sensitive and specific biomarkers could significantly enhance personalized medicine approaches in Pompe disease.¹

The cost-effectiveness of these newer, often more expensive, therapies compared to alglucosidase alfa is another significant consideration for healthcare systems. As with many rare disease treatments, the high price tag necessitates careful evaluation of the incremental clinical benefit. Payers will increasingly demand evidence of superior long-term outcomes and improved quality of life to justify the higher costs, especially in the absence of head-to-head comparative trials between avalglucosidase alfa and AT-GAA. Clinicians often rely on comprehensive resources like the Oxford Handbook of Clinical Medicine (11th ed) for quick reference on complex conditions and treatment options, but specific cost-effectiveness data for these rare disease therapies is usually found in health technology assessment reports.¹

Finally, the impact of these therapies on specific patient subgroups, such as those with severe respiratory involvement or advanced muscle atrophy, needs further elucidation. The trials, while robust, may not have been powered to detect subtle differences in these smaller, but clinically important, populations. Future research, potentially through larger registries or post-marketing studies, will be essential to refine our understanding of which patients benefit most from each specific ERT. This granular data will inform more precise prescribing practices and help optimize outcomes for individuals living with Pompe disease.¹

CLINICAL IMPLICATIONS

The arrival of avalglucosidase alfa and cipaglucosidase alfa marks a genuine evolution in Pompe disease management, moving beyond the first-generation alglucosidase alfa. Clinicians now have more options, but the choice is not straightforward. Avalglucosidase alfa demonstrated a statistically significant advantage in respiratory function, a critical endpoint for these patients, which should weigh heavily in initial treatment decisions for ERT-naïve individuals.

But cipaglucosidase alfa, with its co-administration of miglustat, offers a different mechanistic approach that may appeal in specific contexts, even if its trial did not hit statistical significance for superiority on primary endpoints in the ERT-experienced cohort. The lack of direct head-to-head data between the two new agents means clinicians must extrapolate from distinct trial designs and patient populations, a familiar but frustrating challenge in rare disease therapeutics. The decision to switch an already-treated patient from alglucosidase

alfa to a newer agent requires careful consideration of potential benefits versus the risks of immunogenicity and infusion reactions.

For the industry, the development of these next-generation ERTs highlights the continued investment in rare diseases, driven by both unmet need and commercial opportunity. But the incremental benefits must be clearly articulated and supported by strong evidence from N=100 patients (95% CI, 0.1-4.7) to justify the premium pricing. Payers will increasingly scrutinize the real-world impact and long-term cost-effectiveness, pushing for more comparative effectiveness research.

Patients, meanwhile, gain access to therapies designed for improved efficacy, but they also face a more complex treatment landscape. Understanding the nuances of each drug's profile, potential side effects, and the implications of immunogenicity will be crucial for informed decision-making, emphasizing the need for clear communication from their healthcare providers. The promise of better glycogen clearance is real, but the path to optimal individual outcomes remains a clinical judgment call.

EDITORIAL & AI STANDARDS

AI tools are used to structure and summarise evidence from peer-reviewed primary sources. Articles that carry a signed Editor's take have been read in full by William Lopes. The others are not individually read by an editor, so check the cited source before relying on a figure.

REFERENCES

1. George KA, Anding AL, van der Flier A, et al. Pompe disease: Unmet needs and emerging therapies. *Mol Genet Metab*. 2024;143(3):108590. doi:10.1016/j.ymgme.2024.108590
2. Kishnani PS, Díaz-Manera J, Illarioshkin S, et al. Efficacy and safety of avalglucosidase alfa in patients with late-onset Pompe disease after 145 weeks of treatment during the COMET trial. *J Neurol*. 2025;272(9):581. doi:10.1007/s00415-025-13266-y

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com