

# Addressing Unmet Treatment Needs in POMPE DISEASE

## Therapeutic Strategies for Pompe Disease

### Enzyme Replacement Therapy

#### First-generation ERT

##### Alglucosidase alfa (ALA)

first approved in 2006

#### Second-generation ERT

##### Avalglucosidase alfa (AVAL)

approved 2021/2022 (USA/EU)

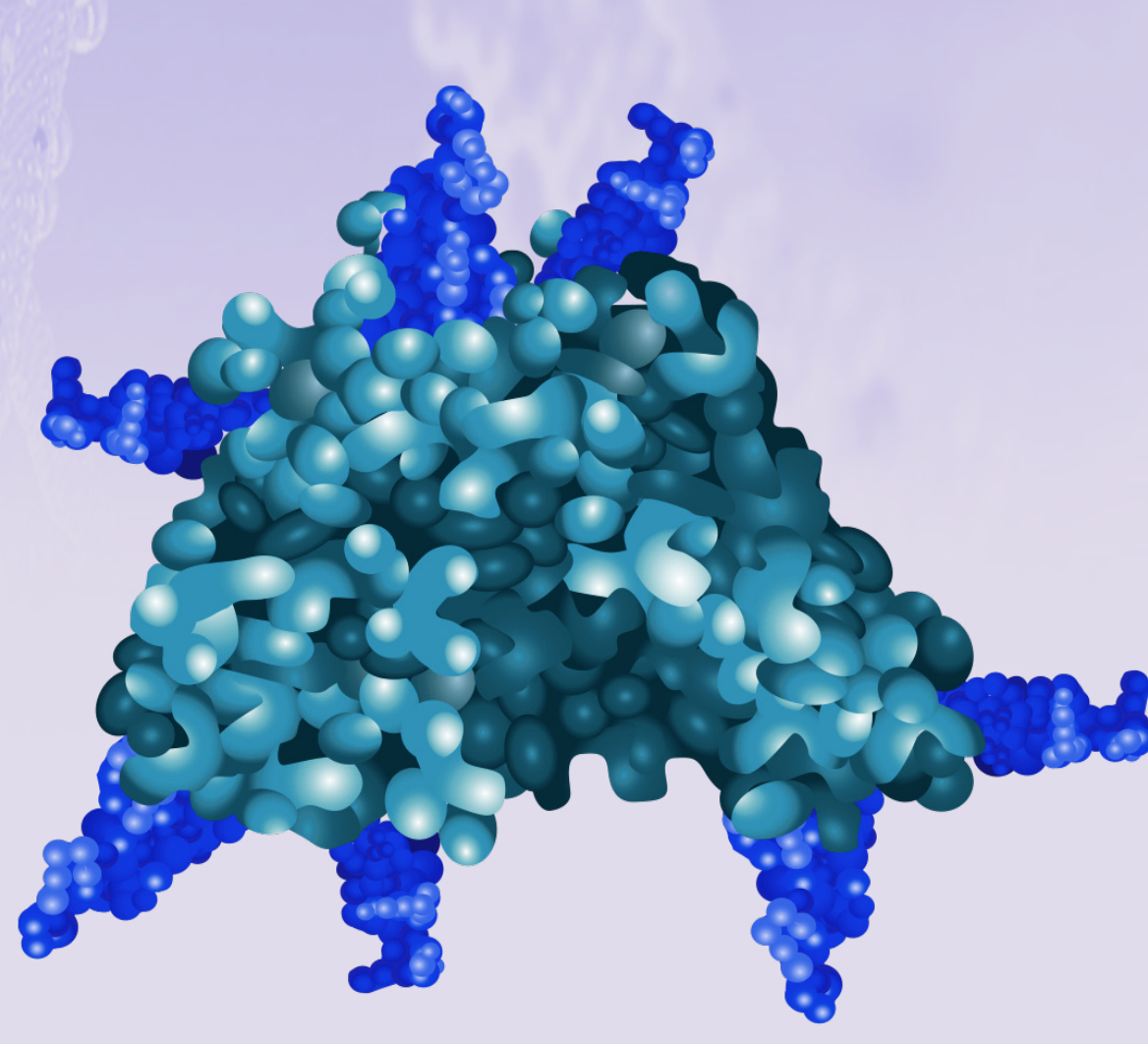
##### Cipaglucosidase alfa with miglustat (CIPA + MIG)

approved 2023 (USA/EU)

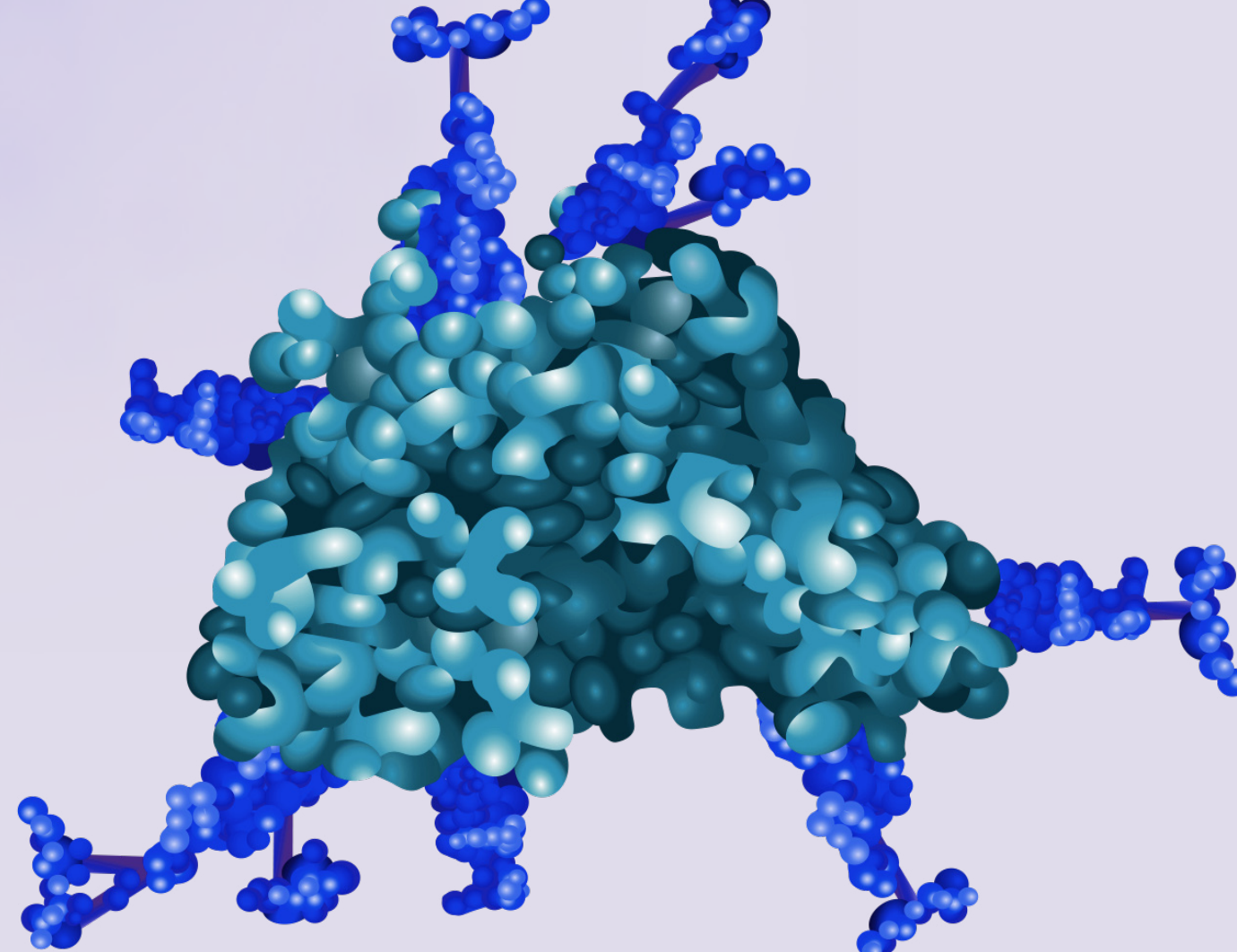
## Second-Generation ERT

### AVAL

- Increased enzyme uptake through greater affinity for the M6P receptors on the cells of target tissues
- Aim is to enhance glycogen clearance and improve the clinical efficacy



ALA

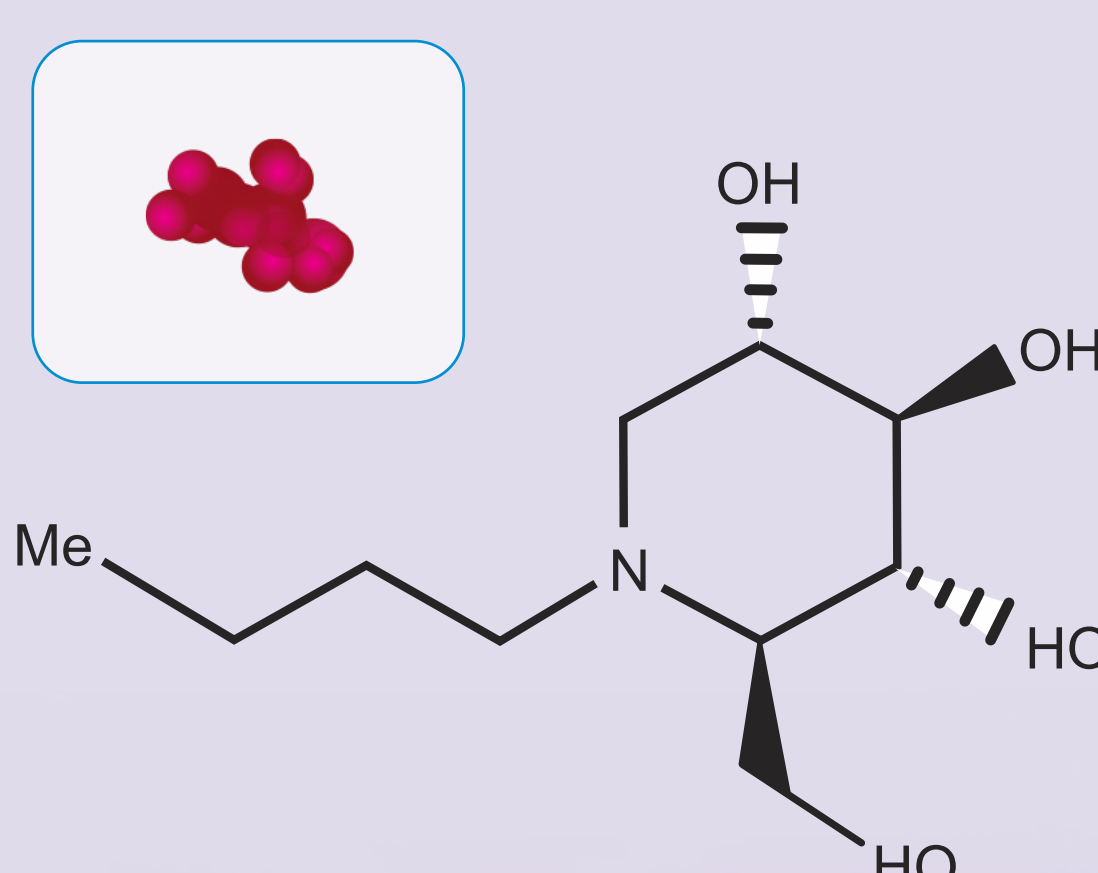
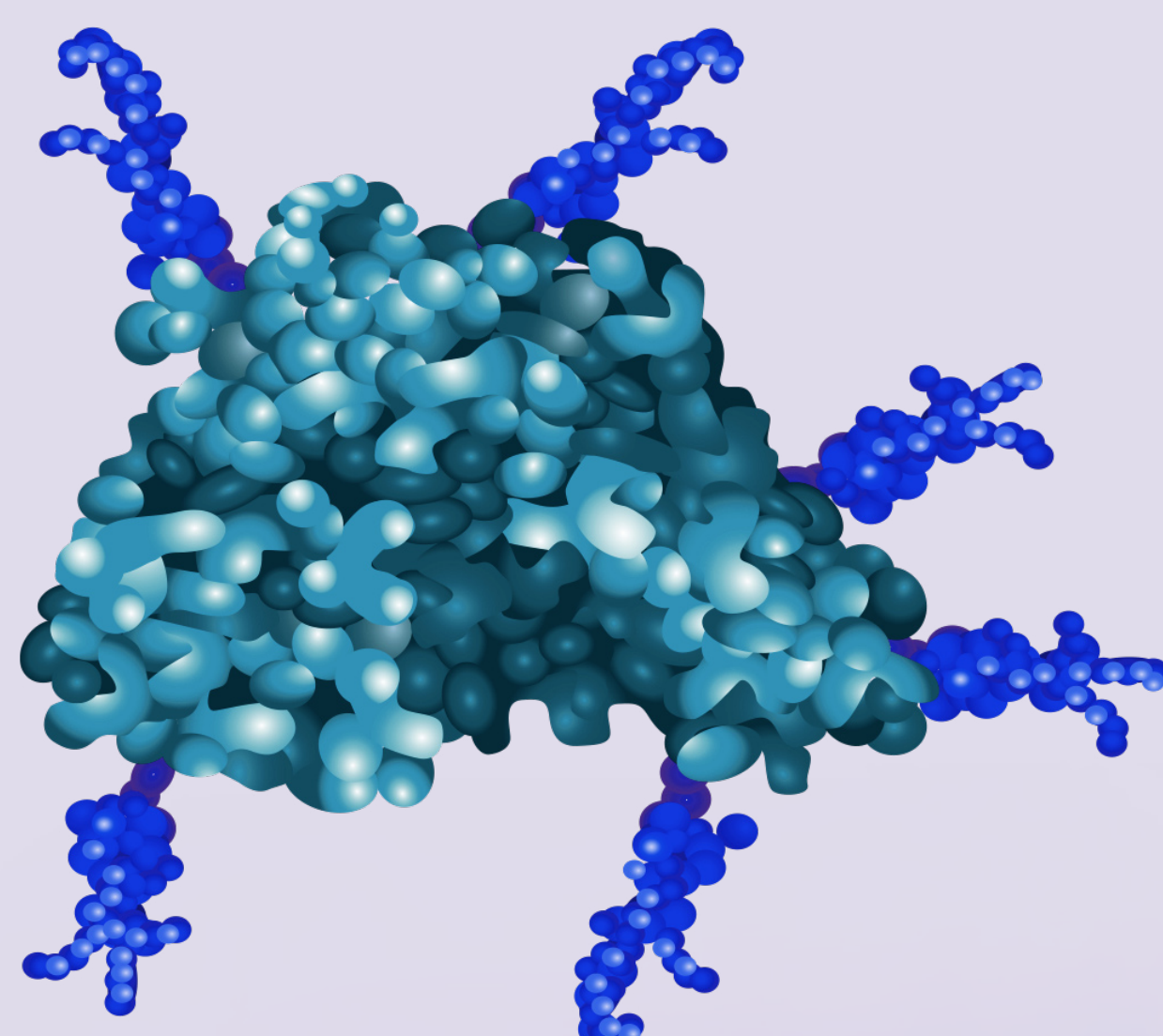


AVAL

### COMET Study

- Treatment-naive patients with LOPD (N=100)
- AVAL led to clinically meaningful improvements in respiratory and motor functions over ALA through week 49
- Statistical analysis showed non-inferiority of AVAL to ALA
- Extension study data showed patients maintained benefits with AVAL and switch patients experienced improvements in respiratory and motor functions
- Similar IgG antidrug antibody responses with both AVAL and ALA

### CIPA + MIG



#### CIPA

- rhGAA with significantly higher M6P
- Approximately 10x higher bis-M6P
- Enables significantly better tissue uptake and lysosomal targeting
- Endogenous addition of structures retains ability for processing to mature and more active form of rhGAA after uptake

#### MIG

- Orally administered iminosugar stabilizer
- Reduces rhGAA protein denaturation and aggregation at neutral pH of plasma
- Stabilizes CIPA in plasma during infusion to provide more active enzyme for uptake into tissues

### PROPEL Study

- Pre-treated and treatment-naive patients with LOPD (N=125)
- CIPA + MIG led to improvements in measures of physical and lung function
- After week 52, the difference between groups in change in sitting FVC percent predicted was significant ( $p = .023$ )
- Extension study data in treatment-experienced patients showed CIPA + MIG maintained benefits and switch patients improved respiratory and motor functions
- Safety profile of CIPA + MIG was similar to that of ALA

### Abbreviations

FVC: forced vital capacity  
ERT: enzyme replacement therapy  
Ig: immunoglobulin  
LOPD: late-onset Pompe disease  
M6P: mannose 6-phosphate  
rhGAA: recombinant human acid alpha-glucosidase

### References

Diaz-Manera J, et al. *Lancet Neurol.* 2021;20:1012-1026.  
Kishnani P, et al. 19th Annual WORLDSymposium. Abstract 202.  
Schoser B, et al. *Lancet Neurol.* 2021;20:1027-1037.  
Schoser B, et al. 19th Annual WORLDSymposium. Abstract LB-59.  
Xu S, et al. *JCI Insight.* 2019;4:e125358.  
Zhou Q, et al. *Bioconjug Chem.* 2011;22:741-751.  
Zhu Y, et al. *Mol Ther.* 2009;17:954-963.