# A disease progression model comparing respiratory and motor decline in people with late-onset Pompe disease treated with cipaglucosidase alfa plus miglustat versus alglucosidase alfa

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## Introduction and objectives

- Late-onset Pompe disease (LOPD) is a progressive and devastating condition caused by a deficiency in GAA, impairing glycogen breakdown in muscle cells and leading to lysosomal glycogen accumulation. Without early and sustained intervention, disease activity persists and irreversible muscle damage affecting mobility, respiration, and daily function can occur. This severely diminishes quality of life and places a substantial burden on individuals, families and caregivers.
- Restoring GAA enzyme activity is central to the effective treatment of LOPD. Alglucosidase alfa (alg) was the first enzyme replacement therapy approved for LOPD.
- Cipaglucosidase alfa + miglustat (cipa + mig) is a two-component therapy designed to deliver more active enzyme to the muscle. Cipa, a second-generation enzyme enriched with naturally-derived bis-M6P—paired with mig, an enzyme stabilizer, work together to improve bioavailability, increase uptake, and ensure complete activation to maximise glycogen clearance. [1,2]
- Whilst there are long-term data available (four years) in the PROPEL OLE, there are limited studies on the lifetime trajectory to mobility and respiratory support in people with LOPD.[3,4] The objective of the analysis was to model long-term LOPD disease progression and provide insight into the potential long-term health outcomes associated with alg and cipa + mig.

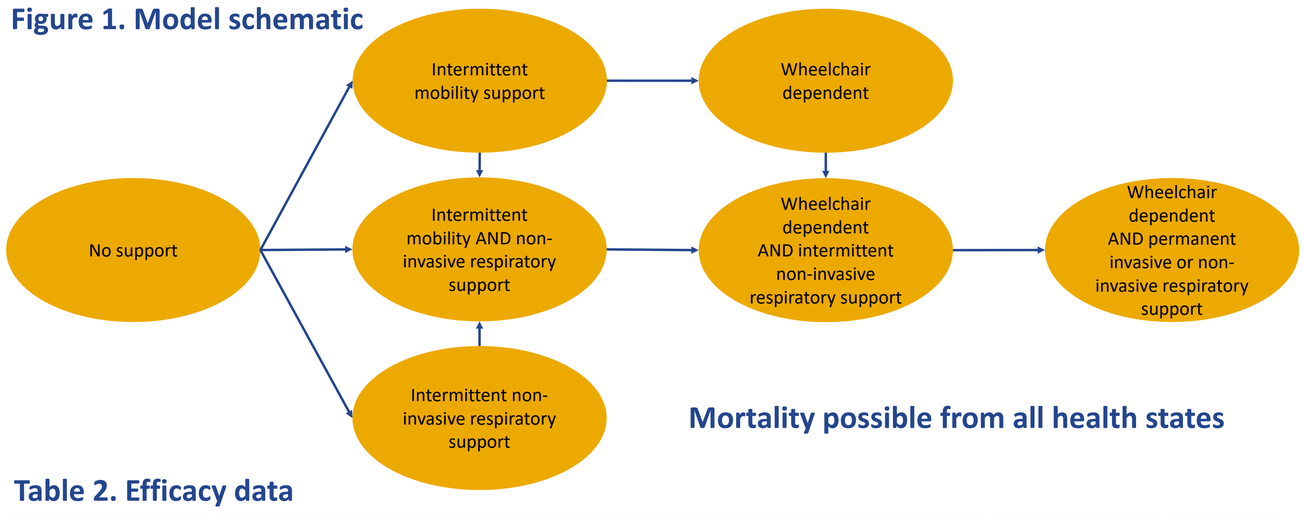
## Conclusions

- Based on the model assumptions, cipa + mig may delay disease progression compared with alg over the lifetime of a patient with LOPD; this would be expected to increase the amount of time spent without mobility and respiratory support dependency.
- Cipa + mig may reduce the overall amount of time a cohort of 100 people would spend wheelchair dependent and requiring invasive respiratory support by 257 and 155 years, respectively.
- The model structure was validated by UK clinical experts and ensured that the main outcome measures for LOPD (%predicted FVC and 6MWD) were fully utilised to accurately capture patient progression.
- The estimated benefit of cipa + mig should be representative of a real-world population and the cohort included both treatment-experienced and treatment-naïve patients.

## Methods

- A patient-level simulation model was developed to compare the effect of cipa + mig with alg on the lifetime disease trajectory of LOPD.
- The model used six-minute walk distance (6MWD) and %predicted forced vital capacity (FVC) to capture the decline in mobility and lung function, respectively.
- Health states were based on the support required (Figure 1) and threshold values were used to determine the point at which each person's condition had declined so that they required mobility support (intermittently or fully dependent) and/or respiratory support (non-invasive or invasive).
- It was assumed 6MWD and %predicted FVC scores would deteriorate progressively, according to the progressive nature of the disease and the requirement for support was associated with an increased mortality risk.
- The probability and/or magnitude of initial improvement and rate of progression differed depending on the treatment received and was informed from clinical trials (Table 2).
- Multiple scenarios were run whereby the progression rates of cipa + mig were assumed to be 25% slower than alg after four years (Scenario 1) or equal to alg after four years (Scenario 2), respectively.
- The annual changes in 6MWD and %predicted FVC were simulated independently using a normal distribution for 10,000 people and the average number of years a person spent in each health state was estimated over a lifetime time horizon.

### Figure 1. Model schematic




### Table 1. Key inputs

| | Value | Source |
|---|---|---|
| Mean (SD): Baseline %predicted FVC | 70.5% (0.20) | PROPEL[3] |
| Baseline 6MWD (m): estimated from correlation | 355.52 | |
| **Thresholds required for mobility and respiratory support** | | |
| Intermittent mobility support, 6MWD (m) | 250 | UK clinical opinion |
| Wheelchair dependent, 6MWD (m) | 75 | |
| Respiratory support dependent, %predicted FVC | 30 | |
| Intermittent respiratory support, %predicted FVC | 40 | NICE HST23 and TA504[5,6] |
| **General population mortality hazard ratios** | | |
| Mean: No mobility or respiratory support | 1 | Güngör[7] |
| Mean (95% CI): Mobility support only | 2.87 (0.98 to 8.36) | |
| Mean (95% CI): Intermittent respiratory support only | 2.05 (0.62 to 6.77) | |
| Mean (95% CI) All other health states | 5.32 (2.25 to 12.56) | |

6MWD: 6-minute walk distance; CI, confidence interval; FVC: Forced vital capacity; HST, highly specialized technologies guidance; NICE, National Institute for Health and Care Excellence; SD, standard deviation

### Table 2. Efficacy data

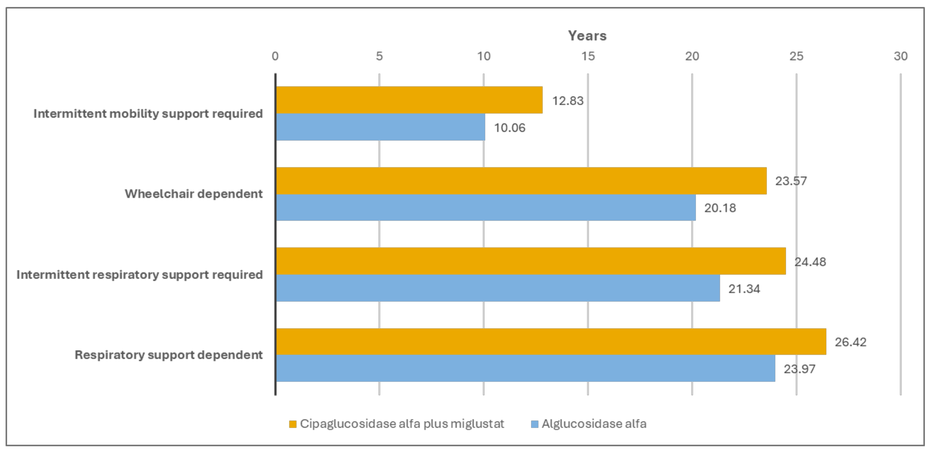
| | Cipa + mig | Source | Alg | Source |
|---|---|---|---|---|
| **Change in 6MWD, mean (SE)** | | | | |
| Baseline to year 1 | 3.5% (0.008) | PROPEL, PROPEL OLE[3,4] | 1.20% (0.011) | PROPEL[3] |
| Year 1 to year 2 | 0.05% (0.01) | | 1.4% (0.003) | Semplicini[9] |
| Year 2 to year 3 | 0% (0.005) | No decline assumed in alignment with outcomes from four-year phase I/II study[8] | | |
| Year 3 to year 4 | 0% (0.005) | | | |
| Year 4 onwards | -2% (0.003) | Relative progression rate compared with alg of 0.85 (assumption supported by UK clinical experts and accepted by NICE) | -2.3% (0.003) | |
| **Change in %predicted FVC, mean (SE)** | | | | |
| Baseline to year 1 | -0.93% (0.007) | PROPEL, PROPEL OLE[3,4] | -3.95% (0.008) | PROPEL[3] |
| Year 1 to year 2 | 0.14% (0.008) | | 0.9% (0.001) | Semplicini[9] |
| Year 2 to year 3 | 0% (0.005) | No decline assumed in alignment with outcomes from four-year phase I/II study[8] | | |
| Year 3 to year 4 | 0% (0.005) | | | |
| Year 4 onwards | -0.8% (0.001) | Relative progression rate compared with alg of 0.85 (assumption validated by UK clinical experts and accepted by NICE)[10] | | |

6MWD: 6-minute walk distance; Alg: alglucosidase alfa; Cipa + mig: cipaglucosidase alfa plus miglustat; OLE: Open label extension; SE, standard error

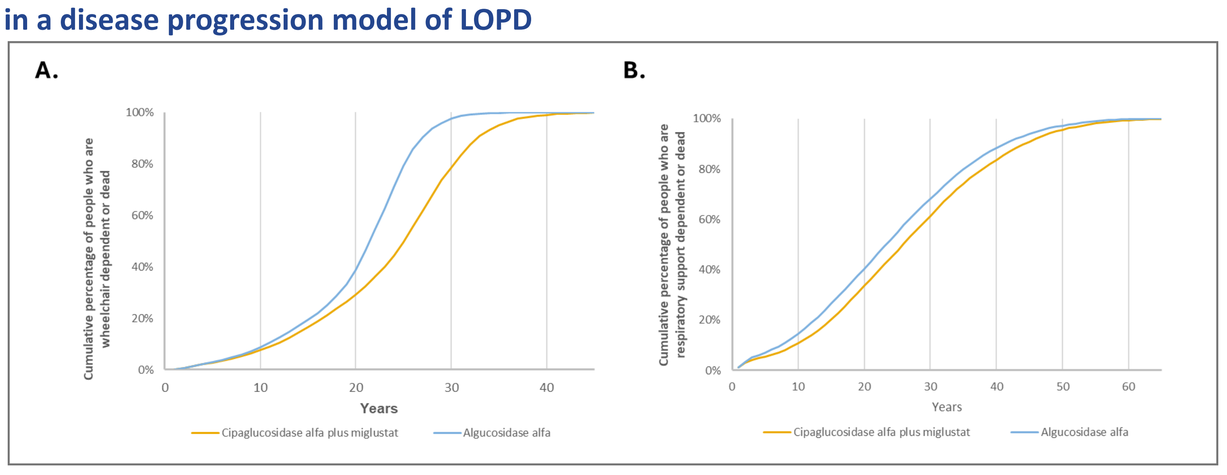
## Results

- Figure 2 depicts the estimated mean time to mobility or respiratory support.
- Based on the model predictions, people receiving cipa + mig require intermittent mobility support and become wheelchair dependent 2.77 and 3.39 years later than those receiving alg, respectively (Scenario 1 – 3.56 and 4.65; Scenario 2 – 1.82 and 1.56).
- People receiving cipa + mig required intermittent respiratory support and became respiratory support dependent 3.14 and 2.45 years later than those receiving alg, respectively (Scenario 1 – 3.77 and 2.92; Scenario 2 – 2.13 and 1.66).
- Figure 3 depicts the cumulative proportion of people requiring mobility and respiratory support throughout the model time horizon.
- The median time to wheelchair dependency is 25 years (25% and 75% percentiles: 18 years and 29 years) and 21 years (25% and 75% percentiles: 16 years and 24 years) for cipa + mig and alg, respectively (as estimated from Figure 3).
- The median time to respiratory support dependency is 25 years (25% and 75% percentiles: 16 years and 35 years) and 23 years (25% and 75% percentiles: 14 years and 32 years) for cipa + mig and alg, respectively (as estimated from Figure 3).

### Figure 2. The mean estimated time to mobility or respiratory support since treatment initiation.




### Figure 3. The cumulative proportion of people in different health states (A) wheelchair dependent or dead; (B) respiratory-support dependent or dead since treatment initiation in a disease progression model of LOPD




## Strengths and limitations

- The model structure utilised the main outcome measures used in LOPD studies (i.e. 6MWD and %predicted FVC), which are the key means of measuring progression according to regulators and the clinical community.
- The model structure and corresponding inputs were reviewed by experienced clinicians and underwent a rigorous assessment process as part a previous HTA appraisal process.
- The estimations for cipa + mig are also generalisable worldwide because the PROPEL trial recruited participants from 24 countries across Europe, North America, Asia and Australia.
- The key limitation of the model is the uncertainty associated with the long-term efficacy of cipa + mig – this was conservatively assumed to be relative to alg due to the absence of alternative information.
- The %predicted FVC and 6MWD were associated with uncertainty because they were informed by proxy conditions and clinician opinions.
- Furthermore, it was not possible to validate the mortality estimates produced by the model against published literature due to a paucity of long-term evidence.

### References

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- M Crabtree, A MacCulloch, N Johnson, V Gielen, and S Clarke are employees of Amicus Therapeutics and hold shares in Amicus Therapeutics.
- S Shohet was an employee of Amicus Therapeutics at the time of the study.
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