Cipaglucosidase alfa with miglustat for treating late-onset Pompe disease [ID3771]

For public – contains no ACIC information

Technology appraisal committee A [03 May 2023]

Chair: James Fotheringham

Lead team: Pratheeban Nambyiah, Richard Ballerand, Steve Edwards

External assessment group: CRD and CHE Technology Assessment Group, University of York

Technical team: Madiha Adam, Alex Sampson, Jo Richardson, Janet Robertson

Company: Amicus Therapeutics

Key clinical questions

- How will the ERT technologies be used in the patient pathway? Will existing ALGLU patients switch to AVAL/CIPA and what would initiate the switch?
- Are AVAL and ALGLU equally relevant as comparators?
- Are the baseline characteristics of PROPEL and ATB200-02 generalisable to NHS clinical practice?
- Is the relative benefit of CIPA + miglustat vs ALGLU in FVC % predicted clinically meaningful?
- Is it plausible that ERT naive people will have a different CIPA treatment effect to ERT experienced?
- Should the total population be considered, or two separate subgroups; ERT-naïve (equivalent to 1L use) and ERT-experienced (equivalent to 2L or later use)?
- If total population is preferred, is the split of patients in PROPEL appropriate? (~77% ERT-experienced)
- What is the best way to specify the treatment effect in the two populations?
- Which hazard ratios for CIPA vs ALGLU and AVAL vs ALGLU should be considered by committee?

1L = 1st line; 2L = 2nd line; ALGLU = Alglucosidase alfa ; AVAL = Avalglucosidase alfa; CIPA = Cipaglucosidase alfa ; ERT=Enzyme replacement therapy; ITC = indirect treatment comparison

Pompe disease

Rare, chronic, progressive, and debilitating genetic disorder

Cause

- Rare, genetic, lysosomal storage disorder, caused by mutated GAA gene
- Leads to accumulation of glycogen in organs and tissues, especially muscles, impairing their function

Prevalence

- ~ 1 in 308,642, (approximately 183 people in England)

Diagnosis/classification

- Infantile-onset Pompe appears in first year of life – muscle weakness, breathing problems and heart defects
- Late-onset typically appears after 12 months - progressive muscle weakness, especially in legs and trunk, including muscles that control breathing. As it progresses, breathing problems can lead to respiratory failure

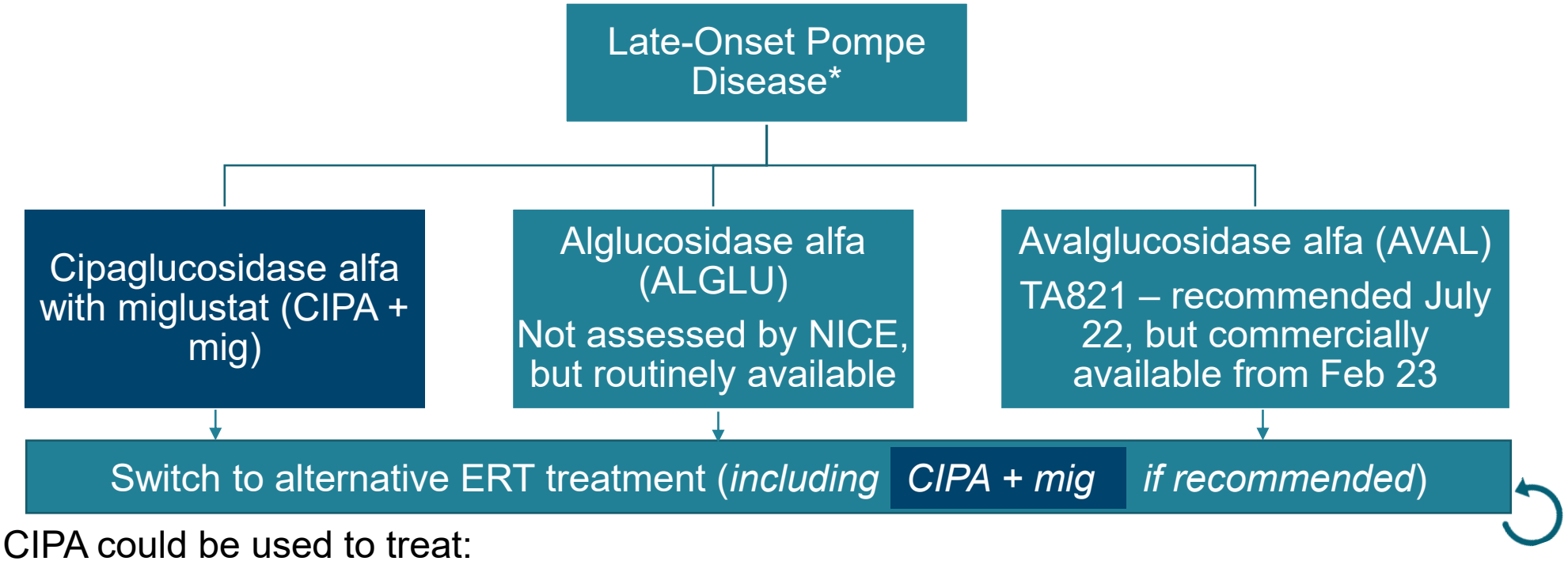
Prognosis

- Both subtypes severely disabling; reduced quality of life for patients and carers
- Reduced life-expectancy to the general population (data limited):
  - IOPD: 2 years if left untreated
  - LOPD: Currently estimated to be 30 years when it presents in children/teenagers; 50 years when it presents in adults

CNS = central nervous system; GAA = acid α-glucosidase; IOPD = infantile-onset Pompe disease; LOPD = late-onset Pompe disease.

Treatment pathway for LOPD

CIPA + miglustat as an alternative to existing standard of care



- CIPA could be used to treat:
  - People newly diagnosed with LOPD
  - People who haven't responded to previous treatment (ALGLU or AVAL)
  - People who have experienced clinical decline following initial response to previous treatment

How will the technologies be used in the patient pathway?
Will existing ALGLU patients switch to AVAL/CIPA?
What would initiate the switch (e.g. FVC % predicted, 6MWT)?

**Marketing authorisation for CIPA + mig includes LOPD only*

Patient perspectives

CIPA + miglustat can improve quality of life by slowing disease progression

Submissions from Pompe Support Network, AGSD-UK, MDUK and patient experts:

- Symptoms have significant impact on physical & psychological wellbeing – decline in mobility and respiratory function affect independence, quality of life & life expectancy
- LOPD also has a significant impact on parents and carers, affecting their mental and physical health, financial security, ability to work and socialise
- Although standard therapies are effective, the response is varied and typically wanes over time. So there's a "desperate and urgent need" for more effective treatments
- People taking CIPA + miglustat reported having more energy and stamina and less fatigue, helping them to live a normal life (climb stairs, get in/out of a car, participate in family life, work, socialise). Also anecdotal reports of reduced brain fog.
- Improved treatments reduce significant need for health, welfare & social care
- Gathering robust, long-term evidence is challenging given the rarity of Pompe, but this shouldn't hinder treatment access
- Some concern about fasting for 2 hours before and after miglustat, and swallowing a pill. But these issues can be mitigated (e.g. dissolving the tablet in water)
- There have been ERT supply issues in the past (due to a single production facility). Having additional treatment option would mitigate risks of supply interruption

"The quality of my life [since taking CIPA] has improved enormously, most notably my lung function has improved. I have more stamina, greatly reduced pain, improved speech, and the effects of the treatment last longer... my partner can continue to work and I maintain my independence and dignity"

"I hope the quality of life that I and others like me have are not undervalued. With adequate technology and equipment and good support and care, I have what I consider to be a high quality of life."

"Even a very small benefit which gives some additional stability in the condition can have a very large effect on actual quality of life."

NICE

AGSD-UK = Association for Glycogen Storage Disease – United Kingdom; ERT = enzyme replacement therapy; LOPD = late-onset Pompe disease; MDUK = Muscular Dystrophy UK

Clinical perspectives

CIPA + miglustat is an evolution in management of LOPD

Submissions from clinical expert and ABN

- CIPA + miglustat would be used to stabilise people that are not, or no longer, responding to existing ERT. It addresses an unmet need. Unclear if it would become 1st line
- Clinical trials on the technology reflect NHS practice and main trial outcomes are those used in clinical practice (6MWT and FVC% predicted)
- Likely that the technology would also lead to improvement in exercise tolerance and reduced fatigue, which may not be fully captured by the QALY approach
- Benefits expected across the Pompe population, both ERT-naïve and ERT-experienced
- Uncertainty about the long-term effectiveness of CIPA but presentations at international meetings suggest that the benefits are durable for at least 2yrs
- Data suggests CIPA is well tolerated and side-effects are similar or less than current SoC
- CIPA + miglustat has same delivery as SoC, plus an oral component. Fasting requirement (2hrs before and after miglustat) may be onerous for some
- Expected that people will attend a specialist centre for initial infusions of CIPA (to observe IARs), before transitioning to homecare. Extra clinical input may be needed due to oral component. Short-term increase in resource use likely as people are moved to the CIPA

"There is an unmet need for people with Pompe disease as after initial improvements on current SOC [ALGLU], for up to 2 years patients deteriorate thereafter."

"The therapy is not a "step change" as the benefits of the technology are modest and the primary outcome measures did not reach statistical significance."

"Most clinicians are considering using the technology in naïve, as well as ERT experienced patients"

6MWT = six-minute walk test; ABN = Association of British Neurologists; FVC = forced vital capacity; IARs = infusion-associated reaction; SoC = standard of care; QALY = quality-adjusted life-year

Equality considerations

Patient Organisation raised the following issue, regarding disease rarity:

- “It’s crucial that the appraisal process does not prejudice access to suitable treatments based on the rarity of the condition and avoids compounding the inequalities faced by people affected

Patient expert raised the following issue regarding disability:

- “Disabled people should have access to as many treatments as practical, even those that might be fractionally better or better tolerated by them to live fulfilling lives as long as they can”

Committee will take into account whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.

Key issues

Key Issue	Resolved?	ICER impact
The inclusion of AVAL as a secondary comparator only and its exclusion from the base case analysis	Yes	N/A
Differences between the ERT-naïve and ERT-experienced populations	Partially – for discussion	Unknown
Uncertainty over the long-term relative effectiveness of CIPA in combination with miglustat	No – for discussion	Large
Use of single arm studies in the indirect treatment comparison	Yes	N/A
Indirect treatment comparison including both ERT-naïve and ERT-experienced participants	Partially – for discussion	Unknown

ALGLU = Alglucosidase alfa ; AVAL = Avalglucosidase alfa; CIPA = Cipaglucosidase alfa ; ERT=Enzyme replacement therapy; ICER = incremental cost-effectiveness ratio

Key issues

Key issue	Resolved?	ICER impact
Cost-effectiveness of comparator treatments	No – out of scope	Out of scope
Improper parameterisation of model	Yes	N/A
Utilities generated using a non-reference case approach	Yes	N/A
Resource use for invasive home mechanical ventilation	No – for discussion	Moderate

ICER = incremental cost-effectiveness ratio

Cipaglucosidase alfa (Pombiliti, Amicus Therapeutics)

Marketing authorisation	• Cipaglucosidase alfa is used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency). • European Commission Decision Reliance Procedure (ECDRP) • EMA granted MA for CIPA in March 2023 • Miglustat CHMP positive opinion received April 2023
Mechanism of action	Cipaglucosidase alfa is an enzyme replacement therapy that mimics the naturally occurring enzyme (alpha-glucosidase) which is lacking in Pompe disease. It is taken with miglustat, which helps the cipaglucosidase alfa enzyme be absorbed more readily by cells.
Administration	CIPA: 20 mg/kg body weight, administered by IV infusion every 2 weeks, alongside miglustat Miglustat – capsules taken orally every 2 weeks, alongside CIPA: • Patients ≥ 50 kg, 4 x 65 mg capsules (260 mg total). • Patients ≥ 30 kg to < 50 kg, 3 x of 65 mg capsules (195 mg total).
Price	• Proposed list price of cipaglucosidase alfa is [redacted] per vial (105mg) • Simple PAS discount agreed with NHS England • Proposed list price of miglustat is [redacted] per bottle of 4 capsules

* based on average participant weight in PROPEL

NICE

CIPA = Cipaglucosidase alfa ; EMA = European Medicines Agency; MA = marketing authorisation; IV = intravenous; PAS = patient access scheme

Decision problem

EAG and company aligned except for comparators

	Final scope	Company (post TE)	EAG comments
Population	People with Pompe disease.	Adults with a confirmed diagnosis of LOPD (GAA deficiency) - aligns with the population in PROPEL and marketing authorisation	Appropriate
Intervention	Cipaglucosidase alfa in combination with miglustat (CIPA + miglustat)	As per NICE final scope.	Appropriate
Comparators	Alglucosidase alfa (ALGLU) Avalglucosidase alfa (AVAL)	As per NICE final scope. (Company says ALGLU is the most relevant comparator as it is established standard of care treatment - AVAL only recently became available).	Both AVAL & ALGLU should be considered
Outcomes	• change in respiratory function • change in motor function • change in muscular function • mortality • immunogenicity response • adverse effects of treatment • health-related quality of life (HRQoL)	All included except mortality - was not assessed in PROPEL due to the low number of expected events	Appropriate

ALGLU = Alglucosidase alfa ; AVAL = Avalglucosidase alfa; CIPA = Cipaglucosidase alfa; GAA = acid α-glucosidase; HRQoL = health-related quality of life; LOPD = late-onset Pompe disease

Key issue: AVAL as a comparator

Company says ALGLU is most relevant comparator, EAG says both AVAL and ALGLU are relevant

Background

- AVAL was licensed in July 22 and recommended by NICE in August 2022 (TA821), but only became commercially available in the UK in Feb 2023 (following company submission)
- Original company base case only included AVAL as a comparator in scenario analysis, not base case

Company

- AVAL has now been included as a comparator in the fully incremental base case analysis
- Company maintains ALGLU is the most relevant comparator as it is established standard of care treatment

Clinical experts

- Difficult to compare CIPA and AVAL as no direct data
- Very fast moving treatment scenario, expect many patients will be switched to AVAL as now available

EAG comments

- Not considering AVAL as a comparator would be inconsistent with NICE scope and current NICE guidance
- Clinical advice suggests it's widely accepted that AVAL will replace ALGLU as preferred 1st line treatment
- Where ERT-experienced patients are considering switching, AVAL represents the only alternative
- Both comparators should be considered

Are AVAL and ALGLU equally relevant as comparators?
Will people on ALGLU be switched to AVAL?

ALGLU = Alglucosidase alfa ; AVAL = Avalglucosidase alfa; CIPA = Cipaglucosidase alfa ; EAG = External Assessment Group; ERT=Enzyme replacement therapy; TA = Technology appraisal

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials for CIPA

	Trial 1 - PROPEL (NCT03729362)	Trial 2 - ATB200-02 (NCT02675465)
Design	Phase III, prospective, double-blind, head-to-head superiority RCT	Phase I/II open-label, fixed-sequence, ascending-dose study
Population	Adults with LOPD, ERT naïve or ERT-experienced (≥2 years on ALGLU)	Adults with LOPD, ERT naïve or ERT-experienced (≥2 years on ALGLU)
Intervention	CIPA with miglustat	CIPA with miglustat
Comparator(s)	ALGLU with placebo	N/A
Duration	12 months	48 months
Primary outcome	6-Minute Walk Test	Plasma GAA activity levels Safety and tolerability (TEAEs)
Key secondary outcomes	Respiratory Function, Muscle Strength, Motor Function, HRQoL, Immunogenicity response, Adverse effects of treatment	Respiratory Function, Muscle Strength, Motor Function, HRQoL, Immunogenicity response, Adverse effects of treatment
Locations	Worldwide (62 sites, including UK)	Worldwide (16 sites, including UK)
Used in model?	Yes	Yes
Quality (EAG)	High quality with low risk of bias	High quality with a low risk of bias

ALGLU = Alglucosidase alfa; ERT = Enzyme replacement therapy; GAA = acid α-glucosidase; HRQoL = Health related quality of life; LOPD = Late-onset Pompe disease; RCT = Randomised controlled trial; TEAEs = Treatment emergent adverse events

Baseline characteristics - PROPEL and ATB200-02

	PROPEL			ATB200-02
	CIPA with miglustat (n = 85)	ALGLU with placebo (n = 38)	Total (N = 123)*	[redacted]
Demographics				
Mean age ([SD])	47.6 (13.25)	45.1 (13.30)	[redacted]	[redacted]
Female, n (%)	49 (57.6)	18 (47.4)	[redacted]	[redacted]
White, n (%)	74 (87.1)	30 (78.9)	[redacted]	[redacted]
ERT status, n (%)				
ERT-naïve	20 (23.4)	8 (21.1)	[redacted]	
ERT-experienced	65 (76.5)	30 (78.9)	[redacted]	
ERT duration (years)				
Mean (SD)	7.48 (3.378)	7.14 (3.635)	[redacted]	
Baseline 6MWD (m)				
Mean (SD)	357.9 (111.8)	350.1 (119.8)	[redacted]	[redacted]
Sitting FVC % predicted				
Mean (SD)	70.74 (19.573)	70.04 (21.301)	[redacted]	[redacted]

Clinical experts: trials have not included advanced patients (full time wheelchair users or ventilated patients) or mild patients

EAG: participants are likely to be representative of patients with LOPD eligible for ERT in clinical practice

Are the baseline characteristics of PROPEL and ATB200-02 generalisable to NHS clinical practice?

* An outlier participant was removed from the efficacy analyses due to deliberate underperformance on the baseline assessments. So, n=123 in the baseline characteristics and safety slides, but n=122 in the efficacy slides

6MWD = six-minute walk distance; EAG = External Assessment Group; ERT: Enzyme replacement therapy; FVC = forced vital capacity; LOPD = late-onset Pompe disease; SD = Standard deviation

PROPEL results – Change in 6MWD from baseline (whole population)

CIPA + miglustat showed greater improvement in 6MWD vs ALGLU

	CIPA + miglustat (n = 85)	ALGLU (n = 37)
Baseline, mean (SD)	357.93 (111.843)	350.95 (121.322)
Change from Baseline at Week 52 (LOCF), mean (SD)	20.79 (42.773)	7.24 (40.277)
MMRM parameter estimation and comparison at Week 52		
LS mean difference (SE)	[redacted]	
95% CI	[redacted]	
2-sided p-value	[redacted]	

Not statistically superior

- People in the CIPA + miglustat arm walked on average 20.8m further at 52 weeks, compared to 7.2m for those in the ALGLU arm
- Improvement of [redacted]% for CIPA + miglustat arm is clinically meaningful according to pre-defined thresholds

NICE

6MWD = six-minute walk distance; LOCF = Last observation carried forward; MMRM = Mixed Models for Repeated Measures; SD = Standard deviation; SE = Standard error; LS mean = Least-squares means

PROPEL results – Change in 6MWD (subgroups)

Different responses in ERT naïve vs ERT experienced, but large uncertainty in the results

Change in 6MWD (m) from baseline to week 52 (ITT-LOCF population)

	6MWD			
	Change from baseline	Mean difference (SE)	95% CI	2-sided p-value
ERT-experienced CIPA + miglustat (n=65) ALGLU + placebo (n=30)	 16.89 -0.02	[redacted]	[redacted]	[redacted]
ERT-naïve CIPA + miglustat (n=20) ALGLU + placebo **(n=7)**	 33.44 38.34	[redacted]	[redacted]	[redacted]
Total PROPEL population CIPA + miglustat (n=85) ALGLU+ placebo (n=37)	 20.79 7.24	[redacted]	[redacted]	[redacted]

- ERT-naïve people had numerically greater improvement with ALGLU compared to CIPA + miglustat, but small patient numbers result in very wide confidence intervals
- ERT-experienced people had greater improvement with CIPA + miglustat compared to ALGLU

6MWD = six-minute walk distance; CI = confidence interval; ERT: Enzyme replacement therapy; SE = Standard error

PROPEL results – Change in FVC % predicted (whole population)

CIPA + miglustat slowed the rate of respiratory decline vs. ALGLU

	CIPA + miglustat (n = 85)	ALGLU (n = 37)
Baseline, mean (SD)	70.74 (19.573)	69.68 (21.475)
Change from Baseline at Week 52, mean (SD)	-0.93 (6.231)	-3.95 (4.892)
Parameter estimation and comparison from ANCOVA		
LS mean difference (SE)	2.66 [redacted]	
95% CI	(0.37, 4.95) ← statistically significant	
2-sided p-value	0.023	

- People in the CIPA + miglustat arm showed a 0.93% decline in FVC % predicted (change from baseline at week 52), compared to a 3.95% decline in the ALGLU arm.
- The least squares mean treatment difference was 2.66%
- Company says this approximate 3% difference for people treated with CIPA + miglustat vs ALGLU indicates a 'clinically meaningful and nominally significant' benefit relative to standard of care.

Is the benefit of CIPA + miglustat in FVC clinically meaningful and robust (given wide CI)?
Is it surprising that FVC% predicted declined but 6MWD increased? Should they be correlated?

NICE

ANCOVA = Analysis of Covariance; CI = confidence interval; FVC = forced vital capacity; LS mean = Least-squares means; SD = Standard deviation; SE = Standard error

PROPEL results – Change in FVC % predicted (subgroups)

Different responses in ERT naïve vs ERT experienced, but large uncertainty in the results

Change in sitting FVC % predicted from baseline to week 52 (ITT-LOCF population)

	FVC			
	Change from baseline	Mean difference (SE)	95% CI	2-sided p-value
ERT-experienced CIPA + miglustat (n=65) ALGLU + placebo (n=30)	0.05 (5.84) -4.02 (5.01)	3.51 [redacted]	1.03 to 5.99	0.01
ERT-naïve CIPA + miglustat (n=20) ALGLU + placebo **(n=7)**	-4.10 (6.53) -3.64 (4.71)	-1.95 [redacted]	-8.93 to 5.03	0.57
Total PROPEL population CIPA + miglustat (n=85) ALGLU+ placebo (n=37)	-0.93 (6.23) -3.95 (4.89)	2.66 [redacted]	0.37 to 4.95	0.02

- ERT-naïve patients appear to respond slightly better to ALGLU compared with CIPA + miglustat
- ERT-experienced patients respond better to CIPA + miglustat

CI = confidence interval; ERT: Enzyme replacement therapy; FVC = forced vital capacity; ITT-LOCF = Intention to treat – last observation carried forward; SE = Standard error

PROPEL results – SGIC (whole population)

More patients said they were improving or stable with CIPA compared to ALGLU

- SGIC gauges the patient-reported impact of treatment on eight endpoints:
  - overall physical well-being
  - effort of breathing
  - muscle strength, muscle function
  - ability to move around
  - activities of daily living
  - energy level
  - muscular pain.

- In all eight domains, higher percentage of participants treated with CIPA + miglustat reported improvement and a lower percentage reported worsening, compared with participants treated with ALGLU

NICE

SGIC = Subject's Global Impression of Change

Propel results - Adverse events (whole population)

CIPA + miglustat has similar AE profile to ALGLU

	CIPA + miglustat (n = 85)	ALGLU (n = 38)
	n (%)	n (%)
Participants who had any TEAE	81 (95.3)	37 (97.4)
Participants who had any serious TEAE	8 (9.4)	1 (2.6)
Participants who had any study drug-related IAR-TEAE leading to study drug discontinuation	[redacted]	[redacted]
Participants who had any serious IAR-TEAE	[redacted]	[redacted]

EAG comments:

- AE profile was similar between CIPA + miglustat and ALGLU, although higher proportion of patients reported a serious TEAE with CIPA + miglustat compared with ALGLU
- Most TEAEs were mild or moderate in severity
- In the CIPA group a small number of patients had a serious IAR-TEAE or a study-drug related IAR-TEAE leading to study drug discontinuation, compared with [redacted] patients in the ALGLU group.

NICE

AE = Adverse events; IARs = infusion-associated reaction; TEAE treatment-emergent adverse event

PROPEL trial – Summary of results

CIPA + miglustat showed benefit over ALGLU for ITT population, but subgroups show mixed results

- CIPA + miglustat showed greater improvement in 6MWD and FVC % predicted vs ALGLU
- SGIC, which is a patient reported outcome, showed greater benefit for CIPA + miglustat vs ALGLU
- Other secondary outcomes (MMT lower extremity score, GSGC total score and PROMIS scores for fatigue and Physical Function) also favoured CIPA + miglustat over ALGLU
- Results of subgroup analysis suggest that:
    - ERT-naïve patients appear to respond slightly better to ALGLU than CIPA + miglustat
    - ERT-experienced patients, who had been on ALGLU for an average of 7.4 years, respond better to CIPA + miglustat.
- But the sample size for ERT naïve people is very small.
- And there are several important differences in the baseline characteristics of the ERT-naïve and ERT-experienced patients ([redacted]).

6MWD = six-minute walk distance; ERT: Enzyme replacement therapy; FVC = forced vital capacity; GSGC = Gait, Stair, Gowers' Maneuver, Chair; ITT = Intention to treat; MMT = manual muscle testing ; PROMIS = Patient Reported Outcomes Measurement Information System; SGIC = Subject Global Impression of Change

ATB200-02 trial – Summary of results

Single arm trial of CIPA + miglustat

- The following mean changes were observed from baseline to month 48:
  - 6MWD increased by [redacted]
  - FVC % predicted increased by [redacted]
- These improvements suggest the effects of CIPA + miglustat persist beyond the 12 months assessed in the PROPEL trial
- However, as this was an uncontrolled study, there is uncertainty over the long-term relative effectiveness of CIPA + miglustat compared with ALGLU.

6MWD = six-minute walk distance; FVC = forced vital capacity

ITC - Multi-level network meta-regression

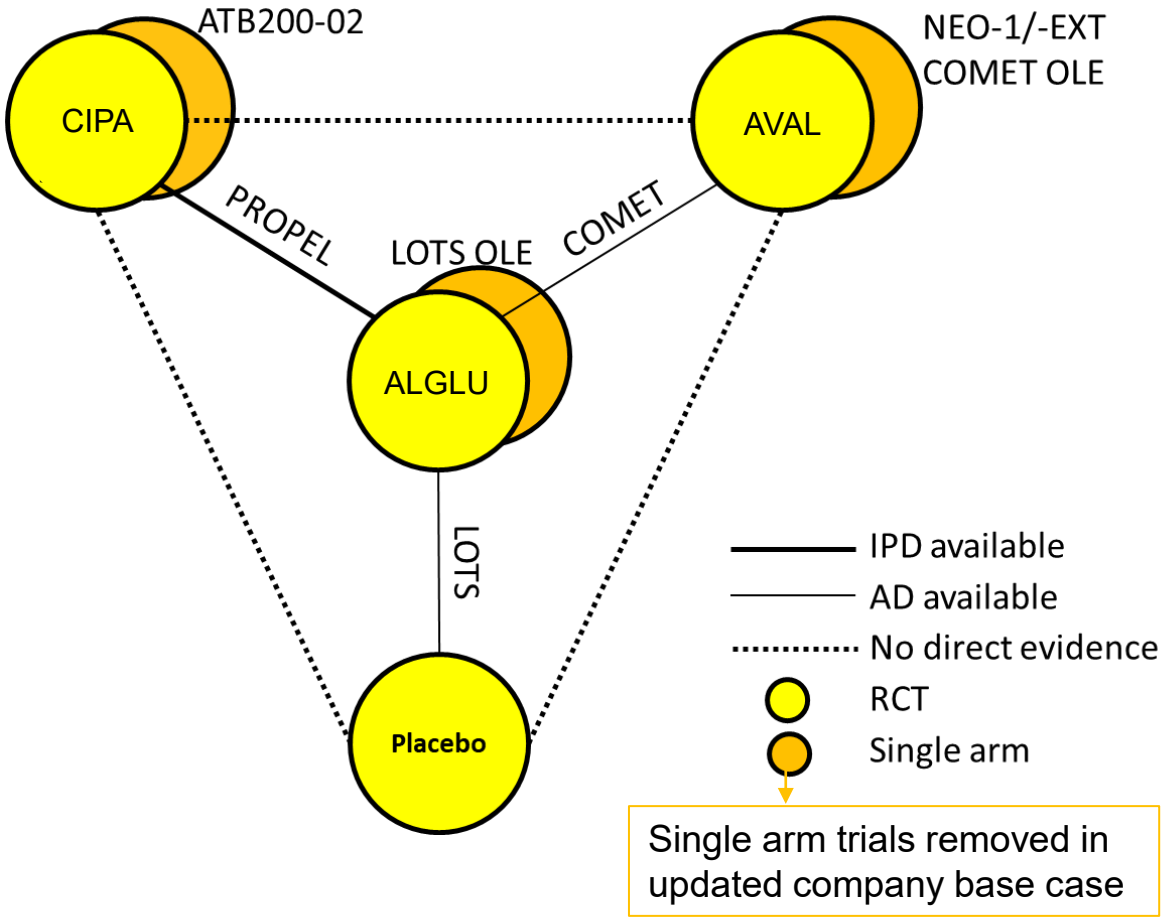
Indirect treatment comparison used in absence of direct data between CIPA & AVAL

- In the absence of direct, head-to-head evidence between CIPA and AVAL, the company conducted Multi-level network meta-regression (ML-NMR)
- 7 trials were identified as suitable for inclusion (including CIPA, ALGLU and AVAL), but 2 single arm trials were excluded from the ML-NMR following technical engagement
- Outcomes considered were 6MWD and FVC % predicted
- The ML-NMR method estimated treatment effects in a mixed population (both ERT-naïve and ERT-experienced)
- Baseline characteristics were adjusted for using individual patient data from PROPEL (age, gender, ethnicity, previous ERT duration, baseline 6MWD and FVC%)

6MWD = six-minute walk distance; ERT = Enzyme replacement therapy; FVC = forced vital capacity

ITC Network Diagram

Indirect comparison included 5 studies, all RCTs



Trial name/author	Design	Interventions	Prior ERT status
PROPEL (NCT03729362)	RCT	CIPA with miglustat ALGLU with placebo	ERT-naïve & experienced
LOTS (NCT00158600)	RCT	ALGU Placebo	ERT-naïve
LOTS OLE (NCT00158600)	Open-label extension	ALGU	ERT-naïve
NEO-1 (NCT01898364) /-EXT (NCT02032524)	Single arm	AVAL	ERT-naïve & experienced
COMET (NCT02782741)	RCT	AVAL ALGLU	ERT-naïve
COMET OLE (NCT02782741)	Open-label extension	AVAL	ERT-experienced
ATB200-02 (NCT02675465)	Single arm	CIPA with miglustat	ERT-naïve & experienced

EAG: SLR was reasonably well conducted and no major concerns about missing studies or the quality of the included studies

RCT = randomised control trial; SLR = systematic literature review;

ITC Results – total population

CIPA showed benefit over ALGLU, but other comparisons are uncertain

Change from baseline in 6MWD at Wk 52

← favours latter Relative effect favours former →

Change from baseline in FVC (% predicted) at Wk 52

← favours latter Relative effect favours former →

- CIPA + miglustat is favoured compared to ALGLU, for both 6MWD and FVC
- All other results have wide confidence intervals and conclusions are uncertain
- EAG considers that the two groups of participants should be considered separately

6MWD = six-minute walk distance; ITC = indirect treatment comparison; FVC = forced vital capacity;
* FVC % predicted was taken from upright in COMET and sitting in PROPEL

Key issue: Difference in benefit by subgroup –clinical/biological plausibility

Mixed views on if/how treatment effect differs in ERT experienced vs ERT naive

Background

- PROPEL included people who'd had ERT previously, and those who hadn't (77% ERT experienced, 23% naive)
- Response to treatment may differ (larger, but delayed, treatment effect for ERT-naïve)

Company

- Value of CIPA + miglustat should be assessed in total population
- Clinical opinion indicates no biological plausibility for a difference in expected benefit between subgroups
- Hypothesis of a larger, but delayed treatment effect in ERT-naïve isn't supported by PROPEL or clinical practice

Clinical experts

- Time on existing ERT matters, as longer duration likely means less capacity to respond to new drugs
- Also loss of muscle associated with age
- ERT naïve patients likely in better health (symptomatic patients already on treatment). They can respond better as still have a lot of glycogen in their muscles, and better basal muscle level
- No clear understanding among research community why ERT naive patients didn't respond better. Counterintuitive

EAG comments

- Clinical advice suggests that these patients will respond differently to treatment (observed in PROPEL);
- Important to appropriately reflect this by considering populations separately.

Is it plausible that ERT naive people will have a different treatment effect to ERT experienced?

ERT = Enzyme replacement therapy; LOPD = late-onset Pompe disease;

Key issue: Difference in benefit by subgroup – trial design

Differences in baseline characteristics create uncertainty about treatment effect

Background

- PROPEL population was mostly ERT experienced (77%) but in COMET (AVAL) participants were all ERT-naïve
- There are differences in the characteristics of ERT-naive and ERT-experienced people

Company

- Value of CIPA + miglustat should be assessed in total population
- In TA821 whole population (naïve & experienced) was considered, despite COMET only including ERT-naïve

Clinical experts

- Definition of 'ERT-experienced' varies between trials (PROPEL ≥2yrs, in COMET patients switched after 49wks)
- Most clinicians considering using the treatment in both populations

EAG comments

- Better evidence on relative effectiveness of AVAL and CIPA in an ERT-naïve population than experienced population due to the absence of ERT-experienced patients in COMET
- Important to appropriately reflect this uncertainty by considering the ERT-naïve and ERT-experienced populations separately. Comparison of a combined ERT-naïve and ERT-experienced population is not appropriate
- As well as differences in treatment effect, also likely to be differences in prognosis. Both will impact ICERs

Should the total population be considered, or two separate subgroups (ERT-naïve and ERT-experienced)? If total population is preferred, is the split of patients in PROPEL appropriate? (~77% ERT-experienced)

ERT = Enzyme replacement therapy; LOPD = late-onset Pompe disease;

Key issue: ITC includes both ERT-naïve and ERT-experienced participants (1)

Reliability of ITC results limited by small sample size for ERT naïve population

Background

- In the original submission, company provided ITC results for the total population only (for AVAL comparison)
- Company's updated base case includes results for the total, ERT-naïve and ERT-experienced populations
- Revised analyses use estimates from ML-NMRs including RCTs only, excluding single arm studies
- Company used ML-NMR to adjust for differences in the populations of studies included in the analysis
- Previous ERT duration was included as a continuous covariate in the regression

Company

- Presenting results for subgroups demonstrates value of the treatment is consistent across subpopulations
- ML-NMR which can adjust for differences in population characteristics and include individual patient data from total PROPEL population (company method) is more appropriate than Bucher analysis (EAG method)

Clinical/patient expert

- Important differences between ERT naïve and ERT experienced patients, but time on ERT is also important
- Including naïve and experienced people seems reasonable as this will address real world clinical question
- Pragmatic approach in absence of any proposed future comparative trials in naïve patients for SoC vs CIPA
- COMET was only naïve patients. Doubtful that CIPA vs AVAL can be robustly compared in experienced patients

ERT = Enzyme replacement therapy; ITC = indirect treatment comparison; ML-NMR = Multilevel Network Meta-Regression; SoC = standard of care;

Key issue: ITC includes both ERT-naïve and ERT-experienced participants (2)

Reliability of ITC results limited by small sample size for ERT naïve population

EAG comments

- ERT-naïve and ERT-experienced patients should be considered separately to reflect potential differences in treatment effect and cost-effectiveness
- The ITC between AVAL and CIPA + miglustat is uncertain as treatment effect comes from different populations.
- While ML-NMR may correct for population differences and estimate effects in each subpopulation, small sample sizes limit reliability of results (only 27 ERT-naïve participants used to inform the meta-regression)
- Uncertainty in the estimates remains given the limited trial evidence available.

What is the best way to specify the treatment effect in the two populations?

ERT = Enzyme replacement therapy; ITC = indirect treatment comparison; ML-NMR = Multilevel Network Meta-Regression;

Key issue: Uncertainty over long term effectiveness of CIPA (1)

There is no comparative data on effectiveness beyond 1yr

Background

- PROPEL trial data are only available for up to 52 weeks follow-up
- Longer term data are available from the ATB200-02 study, but there was no control arm
- Company base case uses [redacted] for CIPA vs ALGLU and [redacted] for AVAL vs ALGLU
- Due to uncertainty over the long term effectiveness of CIPA, different HRs are also explored (CIPA vs ALGLU; 0.3, 0.7 and [redacted], and AVAL vs ALGLU; 0.3, 0.7 & 0.85)

Company

- Expert opinion suggests that people taking CIPA + miglustat will experience disease progression in the long-term, but rate of decline expected to be slightly lower and with delayed waning effect vs ALGLU
- HR of 0.3 explored by the EAG is not be plausible, according to expert opinion. Also said [redacted] is unlikely, but could be used as lower-boundary of plausibility for rate of decline (i.e. minimum HR, conservative scenario)
- Improved survival with CIPA + miglustat continues to counter-intuitively and negatively impact cost-effectiveness estimates. Treatment which extends life vs standard of care should not be unduly penalised due to the cost of ongoing treatment during the period of extended life

Clinical expert

- Poster and platform presentations at international meetings suggest benefits durable over 2yr period (at least)
- Need post-authorization real-world data to understand how CIPA compares to existing ERTs

EAG = External Assessment Group; ERT = Enzyme replacement therapy; HR = hazard ratio;

Key issue: Uncertainty over long term effectiveness of CIPA (2)

There is no comparative data on effectiveness beyond 1yr

Patient experts

- Rarity of disease presents challenges doing large/long-term studies. But short-medium term benefit is clear.
- Given progressive nature of the condition and impact on quality of life, urgent access to treatment needed pending evidence of longer term effectiveness

EAG comments

- Long-term effectiveness of CIPA + miglustat is a significant area of uncertainty. There is limited data to substantiate base case assumptions, which are not informed by any data and so are arbitrary
- Not appropriate to assume that CIPA is superior to AVAL given the limited evidence - no *priori* reason to believe this is the case.
- Assumption is not consistent with results from the ML-NMR which show [redacted]
- Wide range of HRs are plausible given the lack of long-term evidence for both CIPA + miglustat and AVAL
- ATB200-02 showed improvements in 6MWD and FVC % were maintained throughout the follow up period with minimal evidence of decline, suggesting that more optimistic HR explored by EAG could be plausible

Is the assumption that CIPA is more effective than AVAL appropriate?
Which hazard ratios should be considered by committee?

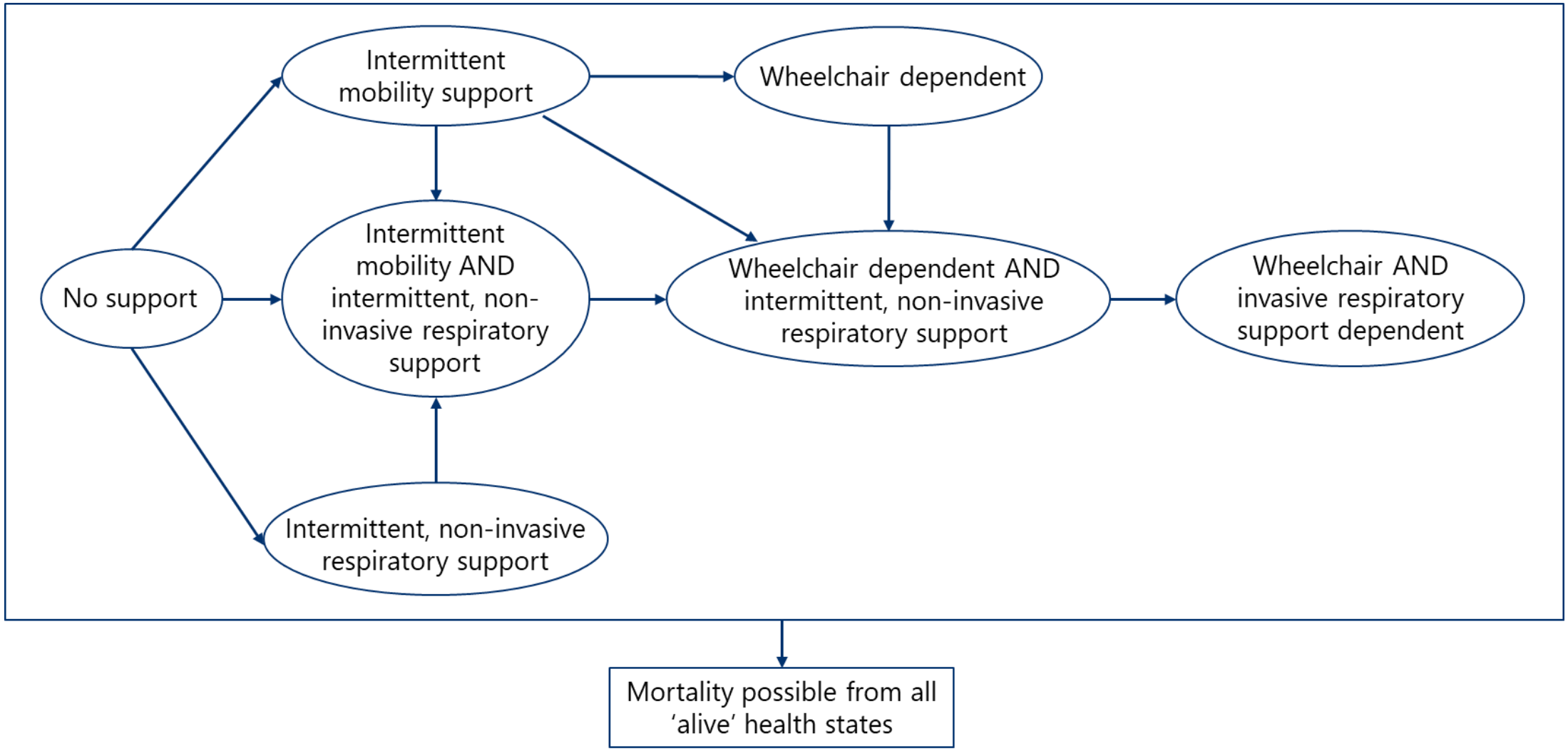
6MWD = six-minute walk distance; EAG = External Assessment Group; FVC = forced vital capacity; HR = hazard ratio; ML-NMR = Multilevel Network Meta-Regression;

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

State transition patient-level simulation model – 7 'alive' health states



Sources of evidence used in the model

Input	Assumption and evidence source
Baseline characteristics	PROPEL (ITT)
CIPA + miglustat efficacy	Baseline to Year 1; PROPEL Year 2+; HR relative to ALGLU
ALGLU efficacy	Baseline to Year 1; ML-NMRs (excluding single-arm trials) Year 2+; Semplicini *et al*. (n=158)
AVAL efficacy	Baseline to Year 1; ML-NMRs (excluding single-arm trials) Year 2+; HR relative to ALGLU
Utilities	PROPEL supplemented by Vignette values
Costs	NHS reference costs 2020/2021, BNF and Personal Social Services Research Unit 2021
Resource use	Clinical opinion and aligned with TA821 where possible
Adverse Events	Not modelled. Similar profile across ERTs, and consistent with TA821

ERT = Enzyme replacement therapy; HR = hazard ratio; ITT = Intention-to-treat; ML-NMR = Multilevel Network Meta-Regression;

Key issue: Resource use for invasive home mechanical ventilation (1)

EAG and company disagree about which source to use for these costs

Background

- EAG concerned that costs for invasive home mechanical ventilation (tracheostomy ventilation) sourced from Noyes et al. in paeds population may be overestimating the cost of invasive ventilation and not generalisable to adult population

Company

- UK clinical opinion suggests that Noyes et al. is likely to be substantially *underestimating* these costs
- Noyes et al. was conducted in UK setting whereas Gajdoš et al. (preferred by EAG) was from Czechia
- Clinical opinion suggest costs would not vary substantially between adult and paediatric populations
- Noyes et al. was included and accepted during the appraisal of AVAL (TA821)
- Scenario presented using Gajdoš et al.

Patient expert

- Medical professionals seem biased towards invasive medical ventilation. Patient expert has been encouraged to consider invasive ventilation a number of times, but from patient expert's perspective, they don't think it provides much benefit but increases risks
- If CIPA can help people continue with non-invasive ventilation for longer, and medical professionals recognise this, delaying the need for invasive ventilation provides a cost and quality of life benefit

EAG = External Assessment Group;

Key issue: Resource use for invasive home mechanical ventilation (2)

EAG and company disagree about which source to use for these costs

Clinical expert

- Vast majority of patients requiring respiratory support can be managed on non-invasive ventilation (NIV), which is considerably cheaper than invasive approaches. NIV costings should be used.

EAG comments

- Conservative approach may be appropriate, given the impact of this parameter (avoiding invasive home mechanical ventilation is a model driver for ALGLU comparison).
- Substantive uncertainty remains - issue is unresolved and unresolvable given available data.

What is the committee's preferred source for invasive home mechanical ventilation costs?

EAG = External Assessment Group; NIV = non-invasive ventilation;

Key issues resolved at Technical Engagement (1)

	Company response	EAG comment
Inclusion of single arm studies in ML-NMR		
• Original company model included 2 single arm studies in the ML-NMR • EAG said not appropriate to include them when a connected network of RCT data is available (although acknowledge the numbers are very small) • Including single arm studies increases sample size, but creates high risk of bias	• ML-NMR informed by only RCTs excludes all data from ERT-experienced participants receiving AVAL. Not generalisable to UK clinical practice, where majority of adults are ERT-experienced. • Acknowledge the trade-off between bias and uncertainty; adopted the conservative approach of excluding single-arm trials from the ML-NMR to minimise bias	• Issue resolved

ERT = Enzyme replacement therapy; ML-NMR = Multilevel Network Meta-Regression;

Key issues resolved at Technical Engagement (2)

	Company response	EAG comment
Improper parameterisation of model		
• Original company model used independent distributions for each model parameter, despite the acknowledgement that model parameters maybe correlated	Variance-covariance matrix generated for key parameters and used to inform the joint sampling for those parameters in the updated base case analysis.	• Changes have been implemented appropriately - issue resolved
Utility values		
• PROPEL could not inform utility values for 'later' health states because most participants hadn't yet reached those health states in the follow-up period. • Company conducted a vignette study to inform values, but EAG concerned the values underestimate utility.	Maintain the validity of Vignette values but aligned with the EAG's model in updated base case (PROPEL supplemented by Vignette values).	• Issue is resolved but uncertainty remains around the appropriateness of values from vignette study. • Vignette utility values seem to be lower than comparable data from other sources (inc. PROPEL)

EAG = External Assessment Group;

Utility values

[redacted] = utility value used in company base case

Health state	Amicus Vignette Study	Published values	PROPEL	TA821 submission
No wheelchair use or respiratory support (0–5 years alive from treatment initiation)	0.61 (0.12)	0.74 (0.15)	[redacted]	0.652
No wheelchair use or respiratory support (6–15 years alive from treatment initiation)		0.70 (0.16)		
No wheelchair use or respiratory support (>15 years alive from treatment initiation)	0.61 (0.12)	0.69 (0.23)	[redacted]	0.652
Intermittent mobility support	0.43 (0.19)	0.67 (0.21)	[redacted]	-
Intermittent, non-invasive respiratory support	0.36 (0.19)	0.61 (0.26)	-	0.614
Intermittent mobility support and intermittent, non-invasive respiratory support	0.29 (0.24)	[redacted]	-	0.545
Wheelchair dependent	0.11 (0.23)	0.146 (0.010)	[redacted]	0.504
Wheelchair dependent and intermittent, non-invasive respiratory support	0.08 (0.22)	[redacted]	-	0.397
Wheelchair and invasive respiratory support dependent	-0.08 (0.22)	[redacted]	-	-

Source: EAG report

Summary of updated company base case assumptions

Assumption	Company base case	Additional EAG scenarios
Use of single arm trials in ML-NMRs	Single arm trials excluded	N/A
Comparators	ALGLU and AVAL (but consider ALGLU the most relevant)	N/A
Utilities	PROPEL supplemented by Vignettes	N/A
Subgroups	Present results for ERT-naïve and ERT-experienced, but prefer whole population	N/A (but prefer subgroups)
Hazard ratios for long-term disease progression	CIPA + miglustat [redacted] than ALGLU (HR=[redacted]) AVAL [redacted] than ALGLU (HR=[redacted])	CIPA vs ALGLU; 0.3 and 0.7 AVAL vs ALGLU; 0.3, 0.7, 0.85
Resource use for invasive home mechanical ventilation	Noyes et al	Noyes, Gajdoš and Nonoyama
Mortality in state 7 (Wheelchair and invasive respiratory support)	Same mortality rate for state 6 (*dependent on wheelchair and non-invasive respiratory support*) & state 7 (*dependent on wheelchair and invasive respiratory support*)	Illustrative scenario provided using higher mortality rate for state 7 (9.92) vs state 6 (5.32). Based on data from traumatic brain injury (fixed ambulatory position with limited mobility)

NICE

EAG = External Assessment Group; ERT = Enzyme replacement therapy; HR = hazard r

Comparison of assumptions with TA821

Assumption	TA821 (AVAL)	ID3771 (CIPA)
Population	IOPD & LOPD	LOPD
Comparators	ALGLU	ALGLU and AVAL
Resource use (costs for invasive respiratory support)	Noyes et al.	• Company prefers Noyes et al. • EAG presented results for Noyes, Gajdoš and Nonoyama (no preference stated)
Health states	5 health states	7 health states
Utilities	COMET (baseline), Pompe disease registry (patient disutilities) and Simon et al. (carer disutilities)	PROPEL supplemented by Vignettes
Population subgroups	Whole population (naïve & experienced) was considered, although COMET only included ERT-naïve	Results provided for whole population and subgroups
Adverse events	Not modelled	Not modelled

EAG = External Assessment Group; ERT = Enzyme replacement therapy; IOPD = infantile-onset Pompe disease; LOPD = late-onset Pompe disease;

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Recap of key questions

- How will the ERT technologies be used in the patient pathway? Will existing ALGLU patients switch to AVAL/CIPA and what would initiate the switch?
- Are AVAL and ALGLU equally relevant as comparators?
- Are the baseline characteristics of PROPEL and ATB200-02 generalisable to NHS clinical practice?
- Is the relative benefit of CIPA + miglustat vs ALGLU in FVC % predicted clinically meaningful?
- Is it plausible that ERT naive people will have a different CIPA treatment effect to ERT experienced?
- Should the total population be considered, or two separate subgroups; ERT-naïve (equivalent to 1L use) and ERT-experienced (equivalent to 2L or later use)?
- If total population is preferred, is the split of patients in PROPEL appropriate? (~77% ERT-experienced)
- What is the best way to specify the treatment effect in the two populations?
- Which hazard ratios for CIPA vs ALGLU and AVAL vs ALGLU should be considered by committee?

1L = 1st line; 2L = 2nd line; ERT = Enzyme replacement therapy; ITC = indirect treatment comparison;

= company base case

Key decisions for committee

1. Population

- Whole population (*based on PROPEL*)
- Population subgroups (consider naïve and experienced separately)

2. HR for CIPA + mig vs ALGLU

- People on CIPA progress 70% slower than on ALGLU (HR = 0.3)
- People on CIPA progress 30% slower than on ALGLU (HR = 0.7)
- People on CIPA progress [redacted]% slower than on ALGLU (HR = [redacted])
- People on CIPA progress at same rate as ALGLU (HR = [redacted])

3. HR for AVAL vs ALGLU

- People on AVAL progress 70% slower than on ALGLU (HR = 0.3)
- People on AVAL progress 30% slower than on ALGLU (HR = 0.7)
- People on AVAL progress 15% slower than on ALGLU (HR = 0.85)
- People on AVAL progress [redacted]% slower than on ALGLU (HR = [redacted])
- People on AVAL progress at same rate as ALGLU (HR = [redacted])

4. Invasive ventilation costs

- **Nonoyama et al.**
- **Gajdoš et al.**
- **Noyes et al.**

5. Mortality in State 7

- **Higher than State 6**
- **Same as State 6**

CIPA is the most cost-effective treatment option in some but not all scenarios

HR = hazard ratio;

NICE National Institute for Health and Care Excellence

Thank you.