Avalglucosidase alfa for treating Pompe disease

AIC and CIC information redacted

Technology appraisal committee A [7 June 2022]

Chair: Jane Adam

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Company: Sanofi Genzyme

NICE

Key clinical issues

Which patients and at what stage would patients benefit from AVAL instead of ALGLU a) late onset b) infantile onset, how does that fit with the licence?

Is the COMET trial (supplemented by NEO1 and NEO-EXT) the best available evidence to inform the LOPD model?

Is the case-note review (Broomfield et al. 2015) the best available data to inform the IOPD economic model?

NICE

Pompe disease

Rare, chronic, progressive, and debilitating genetic disorder

Cause

- Lysosomal storage disorder - mutated GAA gene → accumulation of glycogen in the lysosome
- Glycogen accumulation causes progressive muscle weakness (skeletal, heart and affects the CNS)

Prevalence

- December 2019 ~ 1 in 308,642, (approximately 183 people in England)

Diagnosis/classification

- IOPD typically manifests during the first weeks of life - with hypotonia and respiratory distress
- LOPD after 12 months of age - less cardiac involvement, predominantly affects the lower limbs

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

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

Avalglucosidase alfa (Nexviadyme®, Sanofi Genzyme

Table 1: Technology being appraised

Marketing authorisation	• MHRA innovative medicine designation (September 2020, EAMS positive scientific opinion (5th March 2021) granted for restricted populations:
	  • LOPD in patients who have received ALGLU for ≥2 years.
	  • IOPD in patients ≥1 year old who have received ALGLU for ≥6 months.
	• Final CHMP positive opinion (November 2021) for the broader treatment of Pompe disease (expected MA).

Mechanism of action	• ERT replaces the deficient GAA enzyme, enabling degradation of accumulated lysosomal glycogen.
Administration	20 mg/kg, administered by IV infusion Q2W for patients with LOPD and IOPD. Potential dose increase to 40 mg/kg in IOPD population in non-/limited-responders. Children will require indwelling line.
Price	• List price: ALGLU, £356.06 per 50 mg vial (dose 20mg/kg Q2W); AVAL, £[redacted] per 100 mg vial (dose 20mg/kg Q2W). • Cost per year of AVAL treatment: Adult (78.5 kg), £[redacted]; Child (22.3 kg) £[redacted]. • Simple PAS discount agreed with NHS England.

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; EAMS, early access medicines scheme; EMA, European medicines agency; ERT, enzyme replacement therapy; GAA, alpha glucosidase; IOPD, infantile-onset Pompe disease; IV, intravenous; kg, kilogram; LOPD, late-onset Pompe disease; MA, marketing authourisation; mg, milligram; NHS, National Health Service; PAS, patient access scheme; Q2W, once every 2 weeks.

Treatment pathway
AVAL as an alternative to the existing standard of care

- Current treatment limited to ALGLU
  - **ALGLU not previously assessed by NICE**
- Response can vary between patients
- Well-recognised need for an alternative treatment

Positioning in treatment pathway (IOPD/LOPD)

- AVAL could potentially be used to treat:
  - People recently diagnosed with Pompe disease, i.e. initial treatment
  - People who have not responded to initial ALGLU treatment, i.e. second-line treatment
  - People who have experienced clinical decline following response to initial ALGLU treatment, i.e. second-line treatment

Is AVAL likely to become first-line treatment?

Would it also be appropriate for second line treatment? Would you treat with ALGLU first?

What is the most appropriate position for the technology in the pathway?

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; NICE, National Institute for Health and Care Excellence.

Patient perspectives – LOPD

Symptoms take a physical and mental toll on people

Submissions from patient experts, AGSD UK and MDUK

Living with the condition

- At diagnosis many are already unable to properly walk and some may also already struggle to breathe.
- Most challenging symptoms are muscle weakness, mobility and falls, tiredness and fatigue, and respiratory problems.
- Symptoms and prognosis take a huge toll in terms of their physical and mental wellbeing, and causes considerable anxiety for their future.
- Patients lives are 'shrinking' and improved therapy may come too late.

"My breathing and mobility are both getting worse. I feel worried that I will end up with breathing support fulltime and dread the thought that I won't be able to move around independently"

Current treatment

- Current treatment can help with symptom management but does not treat the underlying cause.
- Patients losing hope as a levelling off in response to standard therapy led to increasing dependence on walking aids and assisted respiration.

"[I worry about] how fast I will decline. Lack of income if things decline quickly. Inability to be the mother my children deserve"

Advantages of the technology

- Among the small number of people with experience of AVAL there was optimism expressed for the future.

Abbreviations: AGSD UK, Association for Glycogen Storage Disease UK; AVAL, avalglucosidase alfa; LOPD, late-onset Pompe disease; MDUK, Muscular Dystrophy UK.

Patient and carer perspectives – IOPD

Symptoms of children also take a substantial toll on their carers

Submissions from AGSD UK and MDUK

Living with the condition

- The most severely affected infants usually present within the first 3 months after birth.
- They have characteristic cardiac problems due to heart enlargement in addition to generalised skeletal muscle weakness, with a life expectancy of less than 2 years if untreated.
- Symptoms and prognosis for children has mental health implications for the parents and carers.

Current treatment

- Current treatment can help with symptom management but do not treat the underlying cause

Advantages of the technology

- For a parent of a child with IOPD, there was a significant reduction in the need for emergency admissions.

"Both my partner's and my mental health have suffered from watching our son deteriorate rapidly before showing some improvement, but the hardest thing is knowing that this condition is going to eventually claim his life."

Abbreviations: AGSD UK, Association for Glycogen Storage Disease UK; MDUK, Muscular Dystrophy UK; IOPD, infantile-onset Pompe disease.

Decision problem
Company analysis in line with the final scope

Table 2: Summary of the decision problem

	Final scope	Company	ERG comments
Population	Children and adults with Pompe disease	As per final scope	None
Intervention	AVAL	As per final scope	None
Comparators	ALGLU	As per final scope	None
Outcomes	• change in respiratory, cardiac, motor and muscular function • mortality • immunogenicity response • adverse effects of treatment • health-related quality of life (for patients and carers)	As per final scope	IOPD: respiratory outcomes limited LOPD: cardiac outcomes not relevant

NICE **Abbreviations:** ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease.

Late-onset Pompe disease

Clinical effectiveness

NICE National Institute for Health and Care Excellence

LOPD clinical trials

COMET: AVAL vs ALGLU in treatment naïve people

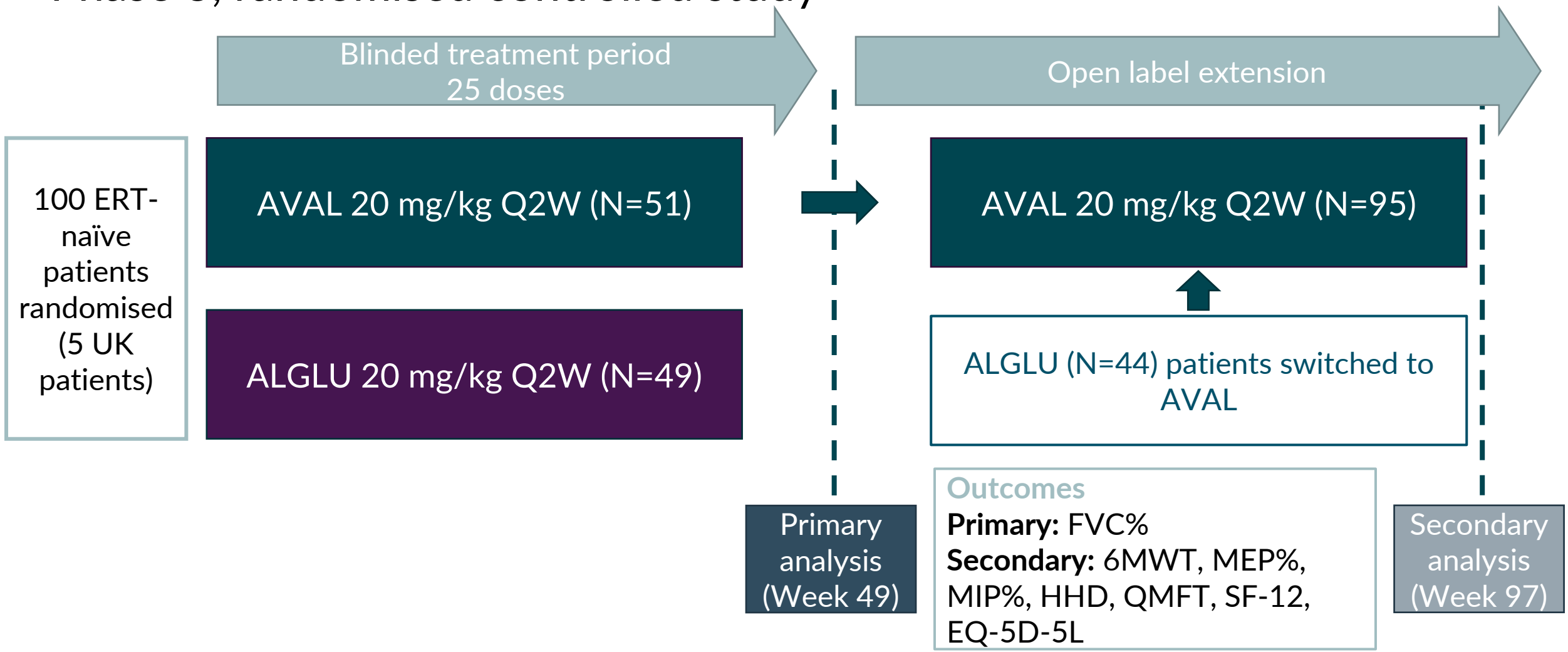
Table 3: Summary of COMET

	COMET (NCT02782741)
Design	Phase 3 non-inferiority RCT
Population	LOPD >3 years old, ERT-treatment-naïve
Intervention	AVAL (N=51)
Comparator(s)	ALGLU N=49)
Duration	49-week blinded period, then open-label extension
Primary outcome	FVC%
Key secondary outcomes	6MWT, muscle strength, motor function and HRQL (SF-12)
Locations	20 countries, incl. UK (N=5)
Used in model?	Yes (magnitude of effect)

Abbreviations: 6MWT, six minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; FVC%, forced vital capacity; HRQL, health-related quality of life; incl., including; kg, kilogram; LOPD, late-onset Pompe disease; mg, milligram; N, number; NA, not applicable; Q2W, every two weeks; RCT, randomised controlled trial; SF-12, Short-Form 12 question utility measure; UK, United Kingdom.

COMET study design

Phase 3, randomised controlled study



Abbreviations: 6MWT, six-minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; EQ-5D-5L, 5-level EuroQol 5-dimension measure; ERT, enzyme replacement therapy; FVC%, forced vital capacity (% predicted); HHD, hand-held dynamometry; kg, kilogram; MEP%, maximum expiratory pressure (% predicted); mg, milligram; MIP%, maximum inspiratory pressure (% predicted); N, number; PAP, primary analysis period; Q2W, every two weeks; QMFT, quick motor function test; SF-12, 12-item short form health survey; UK, United Kingdom.

COMET results – Efficacy: FVC (lung function)

LOPD

Week 49: AVAL non-inferior to ALGLU, not statistically superior (p=0.0626)
Week 97: Improvement with AVAL (statistical significance NR)

Figure 1: COMET mean change in FVC% from baseline

Significant improvement in FVC% with AVAL, but change not significantly better than that with ALGLU

Outcomes used in model (Year 1)

Used to inform initial ventilator status

Would you expect AVAL to present a greater treatment effect than ALGLU?

Would you expect this percentage change to be clinically significant?

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC, forced vital capacity; No., number; NR, not reported; PAP, primary analysis period.

COMET results – Efficacy: 6-minute walk test (mobility)

LOPD

AVAL associated with improved 6MWT*

Figure 2: COMET mean change in 6MWT from baseline

Blinded treatment period | Extension period

Improvement in 6MWT with AVAL, but significance of change than that with ALGLU could not be calculated reliably

Outcomes used in model (Year 1)

Used to inform initial wheelchair status

Would you expect AVAL to present a greater treatment effect than ALGLU?

Would you expect this percentage change to be clinically significant?

Notes: * Significant of change could not be reliably calculated, COMET hierarchical trial design, since superiority was not reached for the primary endpoint (FVC% predicted in the upright position), superiority testing could not be carried out for the remaining endpoints

Abbreviations: 6MWT, six-minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; No., number; NR, not reported; PAP, primary analysis period.

COMET clinical trial results – HRQL

LOPD

Utility improved from baseline on AVAL and ALGLU
No statistical significant difference between treatments

EQ-5D-5L

- Utility values generally higher than baseline at measured timepoints for both treatments
- Data not available for all participants for these analyses
- Large standard deviations
- EQ-5D-5L mapped to EQ-5D-3L, used to inform utility increase for AVAL and ALGLU in model for first year only

NICE

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; EQ-5D-3L, 3-level EuroQol 5-dimension utility score; EQ-5D-5L, 5-level EuroQol 5-dimension utility score; HRQL, health-related quality of life.

COMET clinical trial results – Adverse events
AVAL and ALGLU similarly tolerated

LOPD

Adverse events

- Slightly lower AEs with AVAL
- Four ALGLU patients withdrew due to AEs, none in the AVAL arm
- Most common TEAEs were headache, nasopharyngitis, back pain, fatigue, diarrhoea, nausea

Table 4: Summary of COMET adverse events

Parameter, n (%)	AVAL, N=51	ALGLU, N=49
TEAEs	44 (86.3)	45 (91.8)
Serious TEAEs†	8 (15.7)	12 (24.5)
TEAEs leading to permanent treatment discontinuation	0	4 (8.2)
TEAEs leading to death	0	1 (2.0)

Key: †, Serious TEAE is any untoward medical occurrence that at any dose results in death, or is life-threatening.

Outcome not used in model

Abbreviations: AEs, adverse events; ALGLU, alglucosigase alfa; AVAL, avalglucosidase alfa; n, number; TEAEs, treatment emergent adverse events.

LOPD clinical trials

NEO1/NEO-EXT: Single-arm AVAL in ERT-naïve or after ALGLU

LOPD

Table 5: Summary of NEO

	NEO1 (NCT01898364)	NEO-EXT (NCT02032524)
Design	Phase 1 ascending dose study	Phase 2 extension to NEO1
Population	LOPD ≥18 years, ERT-naïve or previously treated with ALGLU	
Intervention	AVAL (N=24): 5, 10 or 20 mg/kg Q2W	AVAL (N=19) 20 mg/kg Q2W
Comparator(s)	NA	NA
Duration	24 weeks	On-going (data up to week 312)
Primary outcome	Safety and tolerability	
Key secondary outcomes	Change from baseline in FVC % and 6MWT	
Locations	10 sites globally (incl. the UK)	17 site globally (incl. the UK)
Used in model?	Yes (duration of effect)	

Abbreviations: 6MWT, six minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; FVC%, forced vital capacity; incl., including; kg, kilogram; LOPD, late-onset Pompe disease; mg, milligram; N, number; NA, not applicable; Q2W, every two weeks; UK, United Kingdom.

LOPD

NEO1/NEO-EXT clinical trial results – Efficacy

AVAL associated with improved and stable FVC% and 6MWT

Table 6: FVC% predicted, mean change from baseline

Week	Group 1 (ERT-naïve, n=10) All AVAL doses			Group 2 (ERT-experienced, n=14) All AVAL doses		
	N	Mean FVC %	Mean change	N	Mean FVC %	Mean change
Baseline	n=10	[redacted]		n=14	[redacted]	
W25	n=9	[redacted]	2.56	n=13	[redacted]	−0.19
W52	n=8	[redacted]	2.64	n=11	[redacted]	−2.51
W104	n=7	[redacted]	3.11	n=11	[redacted]	−3.79
W208	n=7	[redacted]	1.26	n=10	[redacted]	−1.71
W312	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Mean change denotes mean change from baseline.

Table 7: 6MWT, mean change from baseline

Week	Group 1 (ERT-naïve, n=10) All AVAL doses			Group 2 (ERT-experienced, n=14) All AVAL doses		
	N	Mean 6MWT	Mean change	N	Mean 6MWT	Mean change
Baseline	n=10	[redacted]		n=14	[redacted]	
W25	n=9	[redacted]	1.29	n=13	[redacted]	−0.31
W52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W208	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W312	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Mean change denotes mean change from baseline.

Outcomes used in model (Year 1)

Informing length of response to AVAL treatment

How long would you expect the treatment effect to persist for (AVAL and ALGLU)?

NICE **Abbreviations:** 6MWT, six-minute walk test; ERT, enzyme replacement therapy; AVAL, avalglucosidase alfa; FVC, forced vital capacity; n, number.

Infantile-onset Pompe disease

Clinical effectiveness

NICE National Institute for Health and Care Excellence

IOPD clinical trial

Limited data – not used in model
Only 16 children received AVAL, 6 received ALGLU

Table 8: Summary of mini-COMET

	Mini-COMET (N=22), NCT03019406		
Design	Phase 2, multi-stage, open-label, multicentre, ascending dose study		
Population	Children (aged <18 years) with IOPD previously treated with ALGLU with clinical decline or a sub-optimal response		
Stage	Stage 1 – Children with clinical decline		Stage 2 – Children with suboptimal response
Cohort	Cohort 1 (N=6)	Cohort 2 (N=5)	Cohort 3 (N=11)
Intervention	AVAL 20 mg/kg Q2W	AVAL 40 mg/kg Q2W	AVAL at highest tolerated dose (N=5)
Comparator(s)	NA	NA	ALGLU at current stable dose (N=6)
Duration	25-week primary analysis period, then open-label extension (data for Week 97 in Cohort 3)		
Primary outcome	Safety and tolerability		
Secondary outcomes	Preliminary efficacy		
Locations	International (France, Japan, Taiwan, UK and US)		

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease; kg, kilogram; mg, milligram; N, number; NA, not applicable; Q2W, every two weeks; UK, United Kingdom; US, United States.

Limitations of mini-COMET

IOPD

Small sample size and all pre-treated with ALGLU

- 22 children included in the trial (11 clinical decliners and 11 suboptimal responders)
- Comparative portion made up of 11 suboptimal responders
  - AVAL at highest tolerated dose (N=[redacted]) versus ALGLU at current stable dose (N=[redacted])

High AVAL dose

- Cohort 2 and 3 received 40 mg/kg every 2 weeks – higher than current licenced ALGLU dose

Range of ALGLU doses

- Cohort 3 had children receiving a wide range of ALGLU dosing regimens
  - [redacted]
  - [redacted]

Clinical comments

ALGLU: 20 mg/kg QW for at least first 12 weeks used for newly diagnosed children with IOPD who have significant cardiac disfunction/hypertrophy.

AVAL: Anticipate higher dosing regimen (40mg/kg Q2W, or 20mg/kg QW) would be dose utilised for children with ERT-naïve IOPD at treatment initiation

Outcomes not used in model

Would it be possible to get more data?

NICE

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; kg, kilogram; mg, milligram; N, number; NHS, National Health Service; Q2W, every 2 weeks; QW, every week.

Is there any other data?

Company provided bibliography of missing studies

IOPD

ERG

- ERG counts 37 publications in the company bibliography of 40; remaining 3 not present
- None of the 37 references appear relevant to the decision problem; satisfied but for the missing 3 references

Clinical comments

- Unlikely that any high quality data from patients treated with AVAL has been omitted

Other key data

- Key studies used in the company model:
  - Broomfield et al., 2015:
    - Response of 33 UK patients with infantile-onset Pompe disease to ALGLU
    - Measured overall, ventilator and wheelchair free survival
  - Simon et al., 2019:
    - Health utilities and parental quality of life effects for three rare conditions tested in newborns
  - Pompe registry
    - Sanofi Genzyme data on file

NICE **Abbreviations:** AVAL, avalglucosidase alfa; ERG, evidence review group; SLR, systematic literature review.

Cost effectiveness

Cost-utility analyses

NICE National Institute for Health and Care Excellence

Key issue: Type of economic evaluation

Company prefers cost-comparison analyses and ERG prefers cost-utility analysis

Background

- NICE reference case requests fully incremental cost–utility analysis
- Company presented cost-comparison based on equivalent effectiveness of AVAL and ALGLU (Phase III evidence: AVAL non-inferior to ALGLU) and equivalent or lower cost
- ERG uses cost-utility analysis on the basis that short term benefit likely to impact long term survival:
  - LOPD base case includes AVAL versus ALGLU HR=0.85 (LOPD survival advantage of 3 months)
  - IOPD clinical effectiveness evidence too limited to confirm either equivalence or superiority

Company

- Reiterate preference for cost-comparison, but accept HR=0.85 (in LOPD) and offered AVAL at [redacted]
- LOPD: With survival gain, AVAL [redacted] and [redacted] QALYs than ALGLU
- IOPD: [redacted] and [redacted] QALYs

ERG

- Maintains preference for cost-utility analysis, but notes uncertainty in this

Clinical comments

- Expect AVAL to provide greater efficacy than ALGLU in IOPD; expected to increase HRQL over current care

Does the committee accept that the cost-utility approach is preferable?

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; HR, hazard ratio; HRQL, health-related quality of life; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; NICE, National Institute for Health and Care Excellence; QALYs, quality-adjusted life-years.

Late-onset Pompe disease

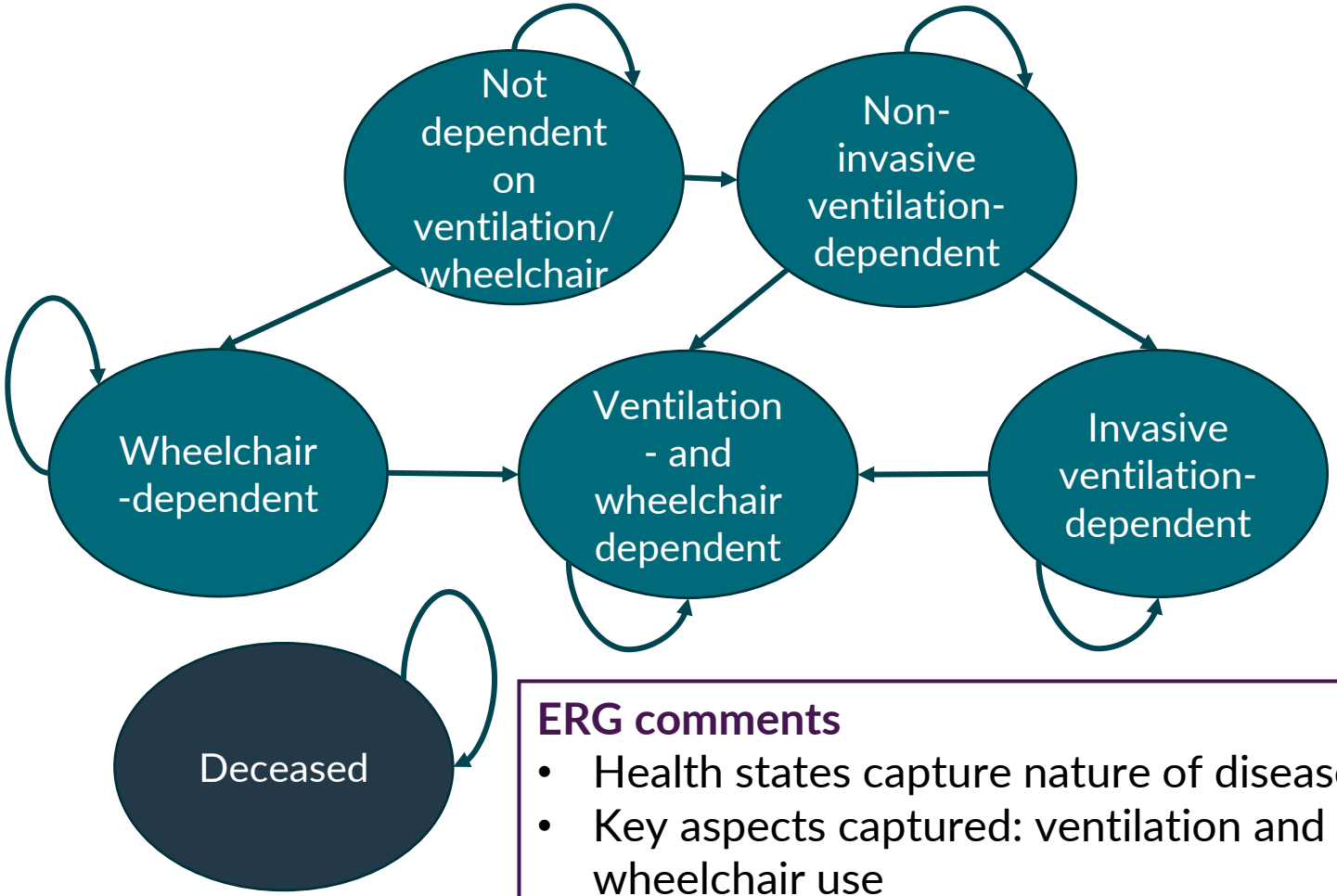
Cost-utility analysis

NICE National Institute for Health and Care Excellence

Company's model overview
Six-state patient-level DICE simulation model

LOPD

Figure 3 LOPD model structure



- Patient-level simulation built using DICE
- 6-state model, using 8 patient 'profiles'
- Patients begin ERT (ALGLU/AVAL) without ventilation or wheelchair use
- Patients transition to:
  - Ventilation states when FVC% falls below a threshold (first non-invasive and then invasive)
  - Wheelchair states after a decline in 6MWT
- Costs, quality of life and mortality captured and updated for each health state

ERG comments

- Health states capture nature of disease
- Key aspects captured: ventilation and wheelchair use
- Simulation can capture heterogeneity and patient history
- DICE model overly complex, difficult to validate, and changes are time consuming

Abbreviations: 6MWT, six minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; DICE, Discretely Integrated Condition Event; ERT, enzyme replacement therapy; FVC%, forced vital capacity; LOPD, late-onset Pompe disease.

How company incorporated COMET evidence into model LOPD

Table 9: Input and evidence sources in company's LOPD cost-effectiveness model

Input	Assumption and evidence source
Baseline characteristics	2,000 simulated patients using COMET data grouped into eight patient 'profiles'
Intervention efficacy	Disease course captured using COMET FVC% and 6MWT Overall survival informed by life tables and adjusted for Pompe disease
Comparator efficacy	
Utilities	COMET (baseline), Pompe disease registry (patient disutilities) and Simon et al. (carer disutilities)
Costs	AVAL: confidential PAS price. ALGLU: £356.06 per 50 mg vial. Administered by IV. Doses rounded up or down to the whole vial
Resource use	Ventilation, wheelchair-related and monitoring/management costs calculated as one-off costs and annual costs
Time horizon and cycle length	Lifetime (60 years) time horizon and monthly cycle length

Abbreviations: 6MWT, six minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC%, forced vital capacity; IV, intravenous; mg, milligram; PAS, patient access scheme; PLD, patient-level data.

Modelling clinical effectiveness

LOPD

Disease course captured through changes FVC% predicted and 6MWT

Figure 4 Predicted trajectory over time (company): a, FVC%; b, 6MWT

Company

- Assumed no clinical improvement during Year 1
- COMET Week 49 results inform change from baseline in FVC% predicted and 6MWT at Year 2
- AVAL: Benefits last [redacted] years (NEO-EXT);
- ALGLU: Benefits last [redacted] and [redacted] years (Pompe registry/clinical opinion)
- Benefits declined linearly at the same rate

ERG

- No conclusions can be drawn on the stability of the treatment effect
- Assume same duration of treatment effect between arms: [redacted] year for FVC% predicted and [redacted] years for 6MWT
- Assumed faster rate of clinical decline for people who discontinue

No critical effect on ICER

Would you expect differences in the duration of treatment effect between ERTs?

NICE

Abbreviations: 6MWT, 6-metre walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; ERT, enzyme replacement therapies; FVC, functional vital capacity; ICER, incremental cost-effectiveness ratio.

Summary of LOPD model, post-technical engagement

LOPD

Company and ERG models are similar

Table 10 Assumptions in company and ERG base case

Assumption	Company base case	ERG base case
Treatment effect duration	[redacted]	[redacted]

- Technology affects **costs** by:
  - [redacted] unit cost of AVAL than ALGLU
  - Lower costs associated with ventilator and wheelchair use due to improved efficacy
- Technology affects **QALYs** by:
  - Increase in life expectancy
  - Lower probability of ventilator and wheelchair use

All other Key Issues resolved or have minimal impact on cost-effectiveness outcomes
(Summary provided in back-up slides)

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; LOPD, late-onset Pompe disease; QALY, quality-adjusted life year

Company results – post-technical engagement

LOPD

Table 11 Incremental base case results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]				
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 12 Probabilistic sensitivity analysis results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]				
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 13 Company scenario analyses

No.	Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£)
1	Company base case	[redacted]	[redacted]	Dominant
2	AVAL plateau period equal to the ALGLU plateau period	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.

ERG results – post-technical engagement

LOPD

Table 14 ERG incremental base case results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]				
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 15 ERG probabilistic sensitivity analysis results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]				
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 16 ERG scenario analyses

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
	ERG's preferred assumptions	[redacted]	[redacted]	Dominant
1	OS AVAL vs ALGLU, HR = 1	[redacted]	[redacted]	Dominant
2	OS AVAL vs ALGLU, HR = 0.7	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Infantile-onset Pompe disease

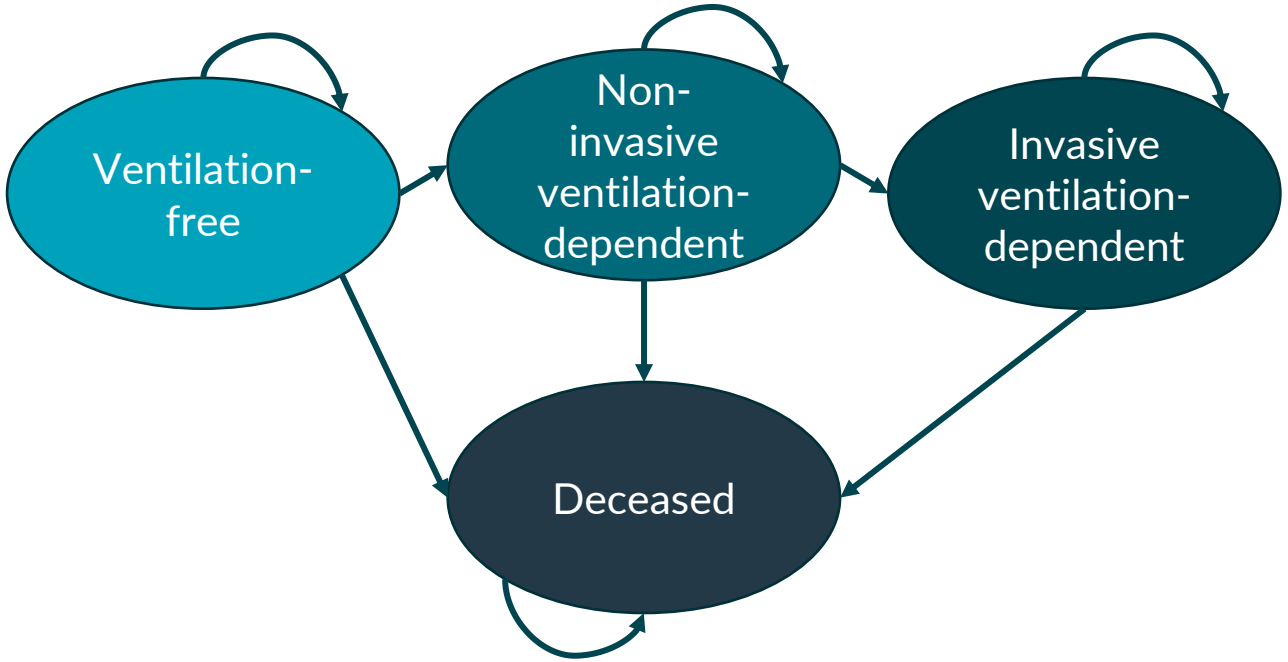
Cost-utility analysis

NICE National Institute for Health and Care Excellence

Company's model overview
Four-state partitioned survival model

IOPD

Figure 4 IOPD model structure



- 4-state partitioned survival model
- Patients begin ERT (ALGLU/AVAL) ventilation free
- Consecutive health states reflect:
  - Changes in lung and motor function
  - Higher costs
  - Lower quality of life
- Costs, quality of life and mortality captured and updated for each health state
- Disease progression modelled with data from Broomfield et al.

ERG comments

- No precedent in Pompe disease but accept approach chosen
- 4 health states reflect disease progression
- Broomfield small population and OS curve may not capture risk of death for children requiring artificial ventilation

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; IVFS, invasive ventilator-free survival; OS, overall survival; VFS, ventilator-free survival.

How company incorporated evidence into model

IOPD

Table 17 Input and evidence sources in company's IOPD cost-effectiveness model

Input	Assumption and evidence source
Baseline characteristics	Broomfield et al.
Intervention efficacy	AVAL and ALGLU equivalent, based on Broomfield et al. OS, VFS and IVFS extrapolated to inform disease progression
Comparator efficacy	
Utilities	Simon et al, utility values for patients/caregivers with mild, moderate and severe Pompe disease ERG prefer alternative source of utility data
Costs	AVAL: confidential PAS price. ALGLU: £356.06 per 50 mg vial. Administered by IV.
Resource use	Ventilation, wheelchair-related and monitoring/management costs
Time horizon and cycle length	50 year time horizon; yearly cycle length

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; IV, intravenous; IVFS, invasive ventilator-free survival; mg, milligram; OS, overall survival; PAS, patient access scheme; UK, United kingdom; VFS, ventilator-free survival.

Key issue: Limited IOPD efficacy and safety evidence

IOPD

Lack of long-term data, uncertainty in long-term efficacy

Background

- Only available comparative evidence for AVAL in the IOPD population is Cohort 3 of mini-COMET
  - Small sample size (n=11 participants) and dose heterogeneity
- A range of equivalence assumptions used for AVAL and ALGLU efficacy due to lack of data

Company

- Mini-COMET showed improvement or stabilisation in children treated with AVAL who weren't responding to ALGLU
- Conservative assumption to assume AVAL has the same efficacy as ALGLU

ERG comments

- Unclear if AVAL would be similar to ALGLU when extrapolated as assumed in use of Broomfield
- ERG's scenario analyses showed significantly higher ICERs if a survival benefit is assumed for AVAL
  - Longer time on treatment → higher treatment cost

Clinical comments

- Efficacy evidence limited, could run treatment-naïve head-to-head study, would take a long time to recruit

Given limited evidence, is the model appropriate for decision making?

NICE

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; UK, United Kingdom.

Modelling overall survival

Equivalent OS assumed by both company and ERG
If OS benefit assumed, major effect on ICER

IOPD

Background
- Mini-COMET showed benefit for AVAL, but no long-term data survival data available

Company
- Equivalence assumed between ERTs, informed by Broomfield 2015
- Broomfield presents survival for 33 UK patients
- Company selected Weibull model

ERG
- Mini-COMET data too limited to conclude equivalence
- All curves are good fit to observed KM data, but Weibull model provides an unrealistic extrapolation
- ERG selected exponential model in base case
- ERG present scenarios will longer OS for AVAL (including HR=0.85 used in LOPD analysis)
- AVAL survival benefits have a major effect on ICER

Is it reasonable to assume equivalence in overall survival?

NICE

Abbreviations: AVAL, avlglucosidase alfa; ERG, evidence review group; ERTs, enzyme replacement therapies; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; UK, United Kingdom.

Summary of IOPD model, post-technical engagement

IOPD

Company and ERG both assume equal efficacy in base case with varying assumptions around dosing and vial sharing

Table 18 Assumptions in company and ERG base case

Assumption	Company base case	ERG base case
Dosing of AVAL in first 12 weeks [Key Issue]	Fortnightly	Weekly dose, as per ALGLU
Vial sharing [Key Issue]	Dose rounded to nearest vial	Dose rounded to nearest vial
OS* [HR Key Issue]	Weibull – HR=1	Exponential – HR=1 (Scenario, HR<1)
Utility estimates*	Simon et al.	Pompe registry
Age-adjusted utility*	Included	Not included – utility values already specified by infant, children and adult

Notes: * Only impact results in scenario where difference in OS is modelled

All other Key Issues resolved or have minimal impact on cost-effectiveness outcomes (Summary provided in back-up slides)

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year

Company IOPD results – post-technical engagement

IOPD

Deterministic results only, no probabilistic results provided

Table 19 Base case deterministic results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]				
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 20 Company scenario analyses (deterministic)

No.	Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£)
1	Company base case	[redacted]	[redacted]	Dominant
2	Exponential distribution used to model OS	[redacted]	[redacted]	Dominant
3	Double dosing for AVAL in the first 12 weeks	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ICER, incremental cost-effectiveness ratio; LYs, life-years; OS, overall survival; QALYs, quality-adjusted life-years.

ERG base case results

IOPD

Table 21 Cumulative results for the ERG's preferred model assumptions

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
1	Company base case	[redacted]	[redacted]	Dominant
2	Double dosing for AVAL in the first 12 weeks	[redacted]	[redacted]	Dominant
3	Dosing estimated by rounding to nearest vial	[redacted]	[redacted]	Dominant
4	Exponential distribution used to model OS	[redacted]	[redacted]	Dominant
5	ERG utility estimates	[redacted]	[redacted]	Dominant
6	Age adjusted utility not included	[redacted]	[redacted]	Dominant
7	ERG's preferred assumptions	[redacted]	[redacted]	Dominant

Notes: Steps 4, 5 and 6 have no impact on model results here as equivalence is assumed.

Table 22 Deterministic incremental base case results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]				
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life-years; OS, overall survival; QALYs, quality-adjusted life-years.

ERG scenario results

Model outcomes extremely sensitive to survival assumptions

IOPD

Table 23 ERG scenario analyses (deterministic)

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
	ERG's preferred assumptions	[redacted]	[redacted]	Dominant
1	OS AVAL vs ALGLU, HR = 0.95	[redacted]	[redacted]	£348,428
2	OS AVAL vs ALGLU, HR = 0.85	[redacted]	[redacted]	£591,310

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life-years.

Other considerations

Equality considerations

- No equality issues raised

Innovation

Company

- AVAL quicker to reconstitute than ALGLU, could reduce vial preparation time freeing up capacity in the NHS, and may encourage further innovation in rare diseases

Clinical experts

- Second-generation ERT, alterations made to the enzyme not especially innovative and are designed to improve the efficiency of treatment rather than being a step change in management
- AVAL addresses the unmet need of the population for whom existing treatment is sub-optimal

Are there any other innovative aspects of the treatment not capture in the QALY calculations?

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; NHS, National Health Service; QALY, quality adjusted life-year.

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Thank you.

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Back-up slides

Key issues

LOPD/IOPD

Table 1 Key issues

Issue	In main deck?	ICER impact
Decision problem		
Cost-comparison or cost-utility analysis? (LOPD/IOPD)	Yes	Small
Clinical effectiveness		
All relevant clinical evidence included? (LOPD/IOPD)	Partially	Unknown
Studies <100 people outside the UK/Netherlands excluded (LOPD)	No	Unknown
Cost effectiveness		
Limited IOPD efficacy and safety evidence (IOPD)	Yes	Unknown
AVAL treatment effect duration uncertain (LOPD)	Yes	Small
Lifetime incremental survival advantage for AVAL (LOPD/IOPD)	Yes	LOPD = Small IOPD = Large
Vial sharing underestimates AVAL treatment costs (LOPD/IOPD)	No	Medium
Increased ALGLU dosing frequency for first 12 weeks, increasing costs (IOPD)	No	Small
ERT dose escalation (IOPD)	No	Unknown

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; UK, United Kingdom.

Key issue: Excluded studies

LOPD

Excluded studies outside of UK and the Netherlands with <100 people

Background

- No studies included if:
  - <100 people conducted outside the UK and the Netherlands
  - Reporting only humanistic outcomes; not SF-36 or EQ-5D
- Rationale for this not reported in company submission, questioned by ERG

Company

- Provided basic details of the 17 non-data extracted studies
- "provided only data on ALGLU or natural history (rather than AVAL) and data from large registries were already available" and "only data most generalisable to the UK were extracted"

ERG

- Agrees with not including ALGLU or natural history studies, but cannot comment on registry data availability
- Unsure on characteristics of studies which affect generalisability to the UK

Clinical comments

- Sample sizes of >100 will be very limited, likely that excluded studies may contain useful information
- UK/Netherlands populations may be similar, but other populations (e.g. US) may also reflect UK population

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Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; EQ-5D, EuroQol 5-dimension utility score; ERG, evidence review group; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; SF-6D, short-form 6-dimension utility score; UK, United Kingdom; US, United States.

Key issue: Vial sharing

LOPD/IOPD

Vials rounded up/down, doses shared across administrations

Background

- Company drug acquisition costs assumes vial sharing of leftover medication, so no wastage stating doses are generally rounded to the whole vial to obtain the 'correct' dose over multiple infusions
- ERG considers this unrealistic and suggested number of vials should be rounded in the model

Company

- Conducted a survey of eight UK treatment centres, experts stated they would round to the nearest vial to avoid vial wastage
- Revised LOPD base case so doses can be rounded up or down to the nearest vial; no change to IOPD model

ERG comments

- Agrees with the company approach to vial wastage (LOPD), supported by clinician survey
- Consider the rounding approach should also be taken for IOPD

Clinical comments

- Use "dose rounding" to utilise a full vial, with alternating dosing to achieve target dose for a patient (i.e. average over alternating doses).

NICE **Abbreviations:** ERG, evidence review group; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; UK, United Kingdom.

Key issue: ALGLU dosing frequency first 12 weeks

IOPD

Company and ERG disagree on initial dosing frequency

Background

- Weekly ALGLU for first 12 weeks, then every other week; company modelled AVAL every other week

Company

- Maintained original position: no evidence or established practice to support initial higher dose of AVAL
- Company included scenario with increased dosing frequency where AVAL remained dominant

ERG comments

- Clinical advice to the ERG expected AVAL to match ALGLU frequency during first three months
- Dosing frequency should be the same for ALGLU and AVAL in the first 12 weeks of the model

Clinical comments

- Newly diagnosed IOPD patients with significant cardiac complications, established higher ALGLU dosing aims to achieve rapid improvement in the cardiac component which would otherwise be fatal
- Anticipated that a higher AVAL dosing regimen (40mg/kg Q2W, or 20mg/kg QW) would be the dose utilised for ERT-naïve IOPD patients at treatment initiation
- Majority of Mini-COMET participants had 40mg/kg Q2W; also dose used for ERT-experienced children switching to AVAL under the EAMS

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; EAMS, early access to medicines scheme; ERG, evidence review group; ERT, enzyme replacement therapy; IV, intravenous; kg, kilogram; mg, milligram; QW, weekly; Q2W, every 2 weeks.

Key issue: ERT dose escalation

IOPD

Impact of different dose escalation approaches is unknown

Background

- Anticipated AVAL licence permits dose escalations for IOPD patients up to 40 mg/kg every other week if inadequate response to 20 mg/kg dose
- Company excluded dose escalations of both drugs from the model; citing equivalence means proportion of patients needing escalations would be the same, offsetting any impact

Company

- Maintains modelling informative scenarios is not possible due to lack of information on how dose escalation would occur in practice

ERG comments

- Equivalence cannot necessarily be assumed; cannot assume proportions requiring increase the same
- Dose escalation should be in scenario analyses (i) ERT-initiation, (ii) Clinical decline (iii) inadequate response

Clinical comments

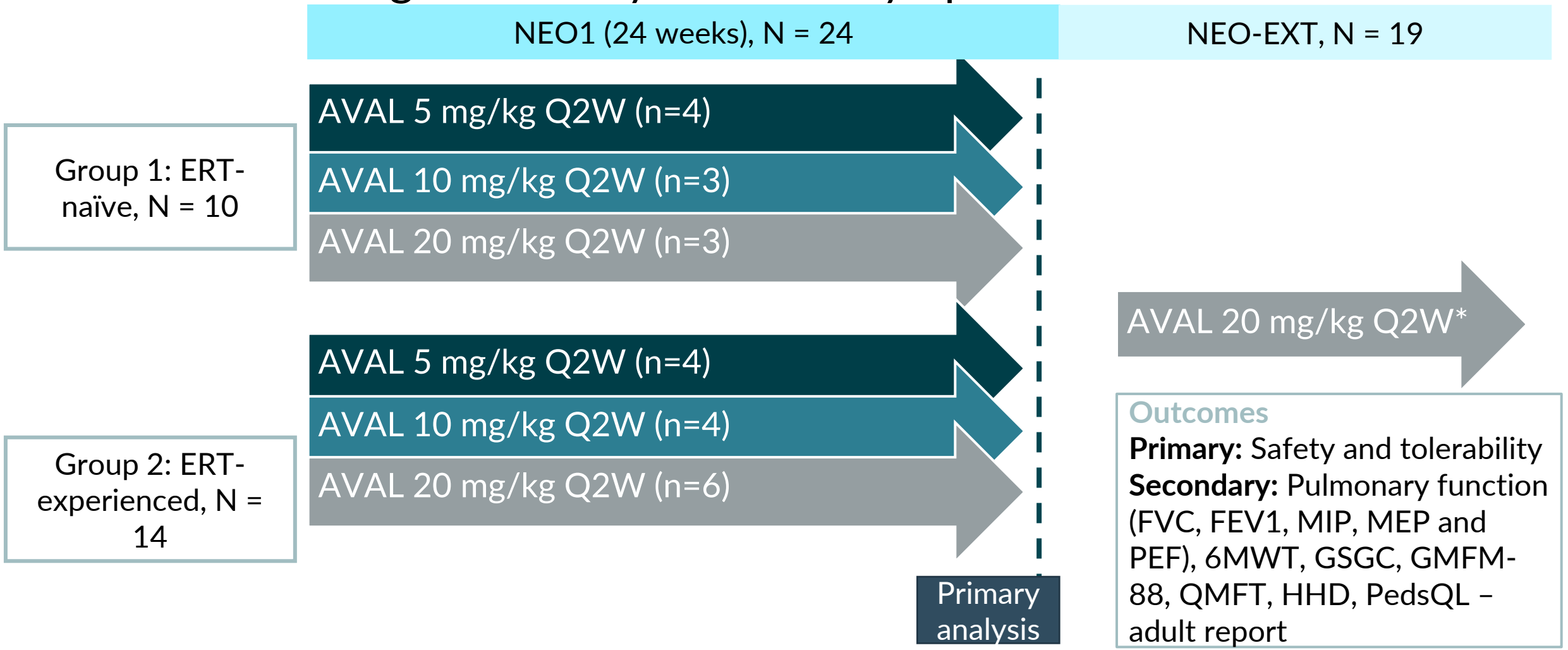
- ALGLU escalation used in clinical practice where suboptimal response or clinical decline; difficult to model dose-escalation for AVAL as likely used in patients already showing suboptimal response
- Clinicians likely to prospectively use higher dose on assumption that this will provide greater benefit

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; kg, kilogram;; mg, milligram.

NEO1 and NEO-EXT study design

LOPD

Phase 1 ascending dose study followed by open label extension



Notes: *All patients transferred to 20 mg/kg dose during 2016.

Abbreviations: 6MWT, six-minute walk test; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; FEV, forced expiratory volume; FVC%, forced vital capacity (% predicted); GSGC, Gait, Stair, Gower's Maneuver, and Chair test; GMFM-88, Gross Motor Function Measure-88; HHD, hand-held dynamometry; kg, kilogram; MEP%, maximum expiratory pressure (% predicted); mg, milligram; MIP%, maximum inspiratory pressure (% predicted); N, number; Peds-QL, paediatric Quality of Life ; PEF, peak expiratory flow; Q2W, every two weeks QMFT, quick motor function test.

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LOPD

LOPD trials baseline characteristics

	COMET (N=100)		NEO1/NEO-EXT (N=24)	
Parameter	AVAL N=51	ALGLU N=49	AVAL: Group 1 (ERT-naïve) N=10	AVAL: Group 2 (ERT-experienced) N=14
Age, mean (SD)	46.0	50.3	44.8	46.7
Age at first symptoms, mean (SD)	32.9	37.7	[redacted]	[redacted]
Predicted FVC (%), mean (SD)	62.5	61.6	68.3	75.4
Distance walked in 6MWT (m), mean (SD)	399.3	378.1	449.2	440.4

Key: ¶n=1

ERG comments

- **COMET:** Generally well balanced; exceptions: AVAL group younger, treated quicker and had better predicted FVC% and 6MWT at baseline. Potentially have a greater chance of showing benefit.
- **NEO:** Younger with better FVC% and 6MWT than COMET. Long-term effect may not be applicable to COMET.
- Both studies excluded people more severely affected by LOPD.

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Abbreviations: 6MWT, six-minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; FVC, forced vital capacity; LOPD, late-onset Pompe disease; m, metre; N, number; SD, standard deviation.

Health related quality of life

LOPD

Utility values adjusted for treatment and disease progression

- Baseline utility for each patient profile assigned using COMET baseline EQ-5D 5L
- Profile utility values adjusted: utility gain for treatment received; disutility for 'complication' health states

Treatment	Utility gain (95% CI)	
ALGLU	[redacted]	
AVAL		
Health state – Patient	**Mean Registry utility (95% CI)**	**Calculated disutility**
Not dependent on ventilator or wheelchair	[redacted]	–
Non-invasive ventilator		[redacted]
Wheelchair-dependent		
Invasive ventilator-dependent		
Ventilator & wheelchair	–	*
Health state – Caregiver (1.72 carers per patient)	**Disutility**	
Mild/moderate	-0.117	
Severe	-0.131	

Notes: *For patients on both a ventilator and wheelchair, the individual disutilities for the ventilator and wheelchair states are additively applied.

- ERG prefer values from the mild states used for the not ventilator-dependent/wheelchair states and moderate to be used for the non-invasive ventilation-dependent health state.

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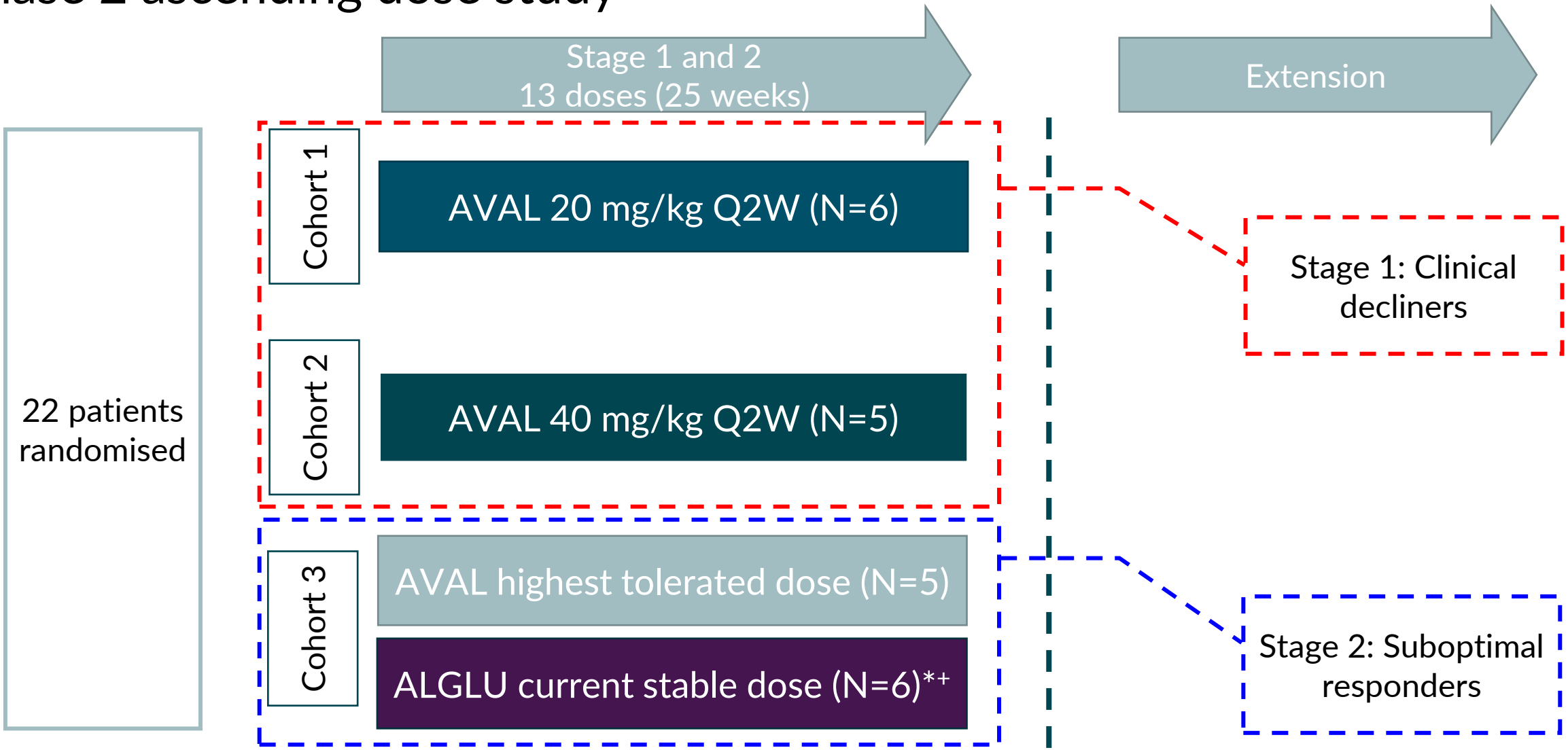
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CI, confidence interval; ERG, evidence review group; EQ-5D 5L, 5-level EQ-5Dl.

Mini-COMET study design

Phase 2 ascending dose study



Notes: *[redacted] of [redacted] treated with ALGLU in Cohort 3 received doses higher than the current maximum dose allowed in the UK. +[redacted] of [redacted] treated with ALGLU in Cohort 3 received weekly dosing.

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; kg, kilogram; mg, milligram; N, number; Q2W, every two weeks; UK, United Kingdom.

Mini-COMET trial baseline characteristics

Lack of IOPD data relevant to UK clinical practice

IOPD

Table 11 Baseline characteristics for intervention and comparator

Parameter	Clinical decliners		Sub-optimal responders	
	Cohort 1	Cohort 2	Cohort 3	
	AVAL 20mg/kg N=6	AVAL 40mg/kg N=5	AVAL HTD N=5	ALGLU CSD N=6
Gender, N (%) male	5 (83.3)	3 (60.0)	2 (40.0)	2 (33.3)
Age at study entry (months), mean (SD)	7.6 (3.4)	8.1 (4.1)	6.9 (2.7)	4.7 (3.2)
Age at diagnosis (years), mean (SD)	1.93 (2.07)	4.29 (3.75)	1.54 (1.49)	5.12 (5.46)
Age at first symptoms (months), mean (SD)	1.23 (1.70)	3.33 (2.93)	0.18 (0.41)	1.79 (1.72)
Predicted FVC (%), upright, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Distance walked from 6MWT (m), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

ERG comments

- Lack of treatment-naïve data, unlikely to represent UK clinical practice should AVAL be approved
- Clinicians are likely to use the weekly 40 mg/kg dose for AVAL in clinical practice
- ALGLU dosing in Cohort 3 unbalanced, [redacted] of [redacted] received doses exceeding maximum dose used in the UK

Abbreviations: 6MWT, six minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CSD, current stable dose; FVC%, forced vital capacity; kg, kilogram; HTD, highest tolerated dose; IOPD, infantile-onset Pompe disease; mg, milligram; m, metre; N, number; SD, standard deviation; Q2W, every two weeks.

Adverse events – Mini COMET
AVAL similarly tolerated as ALGLU

IOPD

- AE incidence was comparable between the two treatment arms in Cohort 3.
- The highest proportion of TEAEs experienced by patients were observed in the [redacted] organ class.
  - [redacted], [redacted], and [redacted] were the most common by preferred term.

Parameter, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
TEAEs	5 (83.3)	5 (100)	5 (100)	5 (83.3)
TEAEs potentially related to study treatment	0	2 (40)	1 (20.0)	1 (16.7)
TESAEs[†]	1 (16.7)	3 (60.0)	0	2 (33.3)
TESAEs potentially related to study treatment	0	0	0	0
Severe TEAEs[†]	0	2 (40.0)	0	1 (16.7)
Severe TEAEs potentially related to study treatment	0	0	0	0
Adverse event of special interest	0	2 (40.0)	1 (20.0)	1 (16.7)
Protocol-defined IARs	0	2 (40.0)	1 (20.0)	1 (16.7)
Algorithm-defined IARs	0	2 (40.0)	1 (20.0)	1 (16.7)

Abbreviations: AEs, adverse events; ALGLU, alglucosigase alfa; AVAL, avalglucosidase alfa; IARs, infusion adverse reactions; n, number; SAEs, serious adverse events; TEAEs, treatment emergent adverse events;