NICE National Institute for Health and Care Excellence

Slides for public observers

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

Chair's presentation

2nd Appraisal Committee Meeting

Chair: Stephen O'Brien
ERG: Kleijnen Systematic Reviews
Technical team: Catie Parker, Caron Jones, Jasdeep Hayre
Company: Bioprojet UK

13th October 2021

Pitolisant hydrochloride is not recommended, within its marketing authorisation, to improve wakefulness and reduce excessive daytime sleepiness in adults with obstructive sleep apnoea whose sleepiness has not been satisfactorily treated by primary obstructive sleep apnoea therapy such as continuous positive airway pressure (CPAP), or who cannot tolerate it.

Why the committee made these recommendations

- Trials may have excluded people who would be eligible for pitolisant hydrochloride in the NHS in England
- Uncertainty around improvement in quality of life
- Potential placebo effect not explored sufficiently
- Uncertain assumptions about reduced risk of cardiovascular events

Key issues

Issue		Description	Impact	Status
1	Placebo effect	• Hawthorne effect (*company ACD model*) • Regression to the mean • True placebo effect		**Unresolved**
2	Utility values	• ESS mapped to EQ-5D using McDaid (*company base case*) • EQ-5D values from HAROSA trials		**Unresolved**
3	ACD model	• No probabilistic sensitivity analysis • No drug wastage included • BSC transition probabilities • Other ERG issues	**N/A**	**Unresolved**
4	Adherence to CPAP	• Impact of pitolisant treatment on CPAP use		**Partially resolved**

 **Model driver**  **Unknown impact**

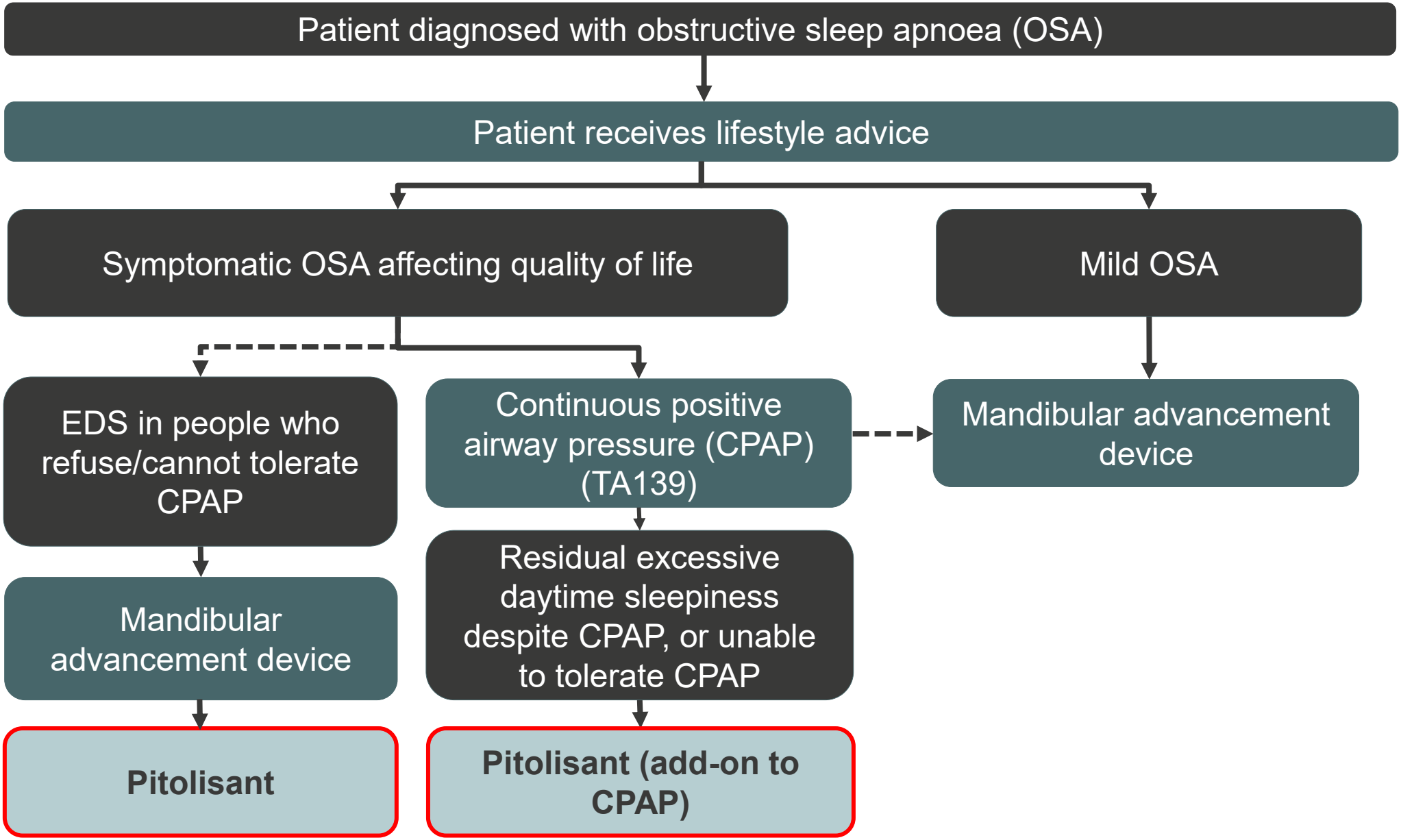
NICE ACD, appraisal consultation document; BSC, best supportive care; CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale

Pitolisant (Ozawave, Bioprojet UK)

Mechanism of action	Orally active histamine H3-receptor antagonist/inverse agonist that enhances the activity of brain histaminergic neurones. It also modulates neurotransmitter systems, increasing acetylcholine, noradrenaline, and dopamine release in the brain.
Marketing authorisation (positive CHMP May 2021)	Indicated to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnea (OSA) whose EDS has not been satisfactorily treated by, or who have not tolerated, OSA primary therapy such as continuous positive airway pressure (CPAP).
Dosage and Administration	Pitolisant should be used at the lowest effective dose, depending on an individual's response and tolerance, according to an up-titration scheme, without exceeding 18 mg/day: Initial dose of 4.5 mg per day can be increased to 9 mg (two 4.5 mg tablets) per day in week 2. The dose can be titrated up or down from week 3 (to one 18 mg tablet) or down to 4.5 mg per day.
List price	Wakix NHS indicative price £310 per 30 tablets, Ozawave [redacted] [redacted] for 30 tablets, [redacted] for 12 month supply (company submitted PAS, but it has not yet been approved by NHS England)

CHMP, Committee for Medicinal Products for Human Use; PAS, patient access scheme

Treatment pathway – current and proposed



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EDS, excessive daytime sleepiness

HAROSA I & II summary

Randomised, double-blind, placebo-controlled trials with open label phases

Population*

Intervention
(12-week double blind phase)

Open label phase

HAROSA I

- Adults who had **CPAP** for ≥3 months but still had EDS
- Baseline ESS ≥12

Pitolisant (n=183)
Placebo (n=61)
→ Pitolisant (n=199)

HAROSA II

- Adults who had **refused CPAP** and still had EDS
- Baseline ESS ≥12

Pitolisant (n=201)
Placebo (n=67)
→ Pitolisant (n=236)

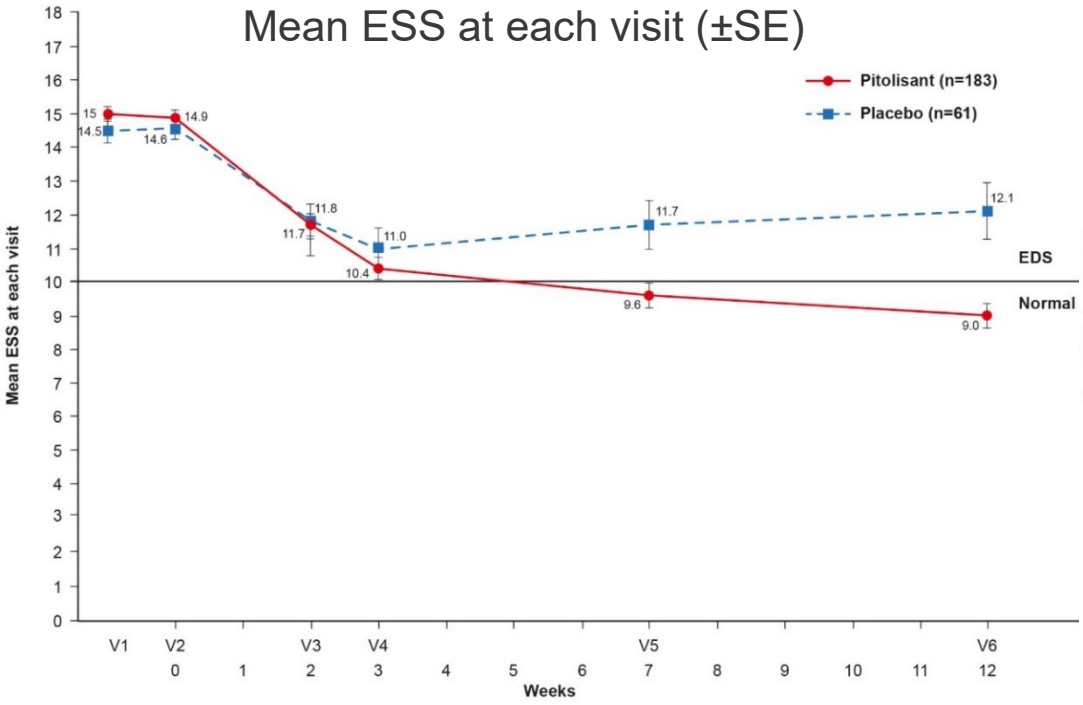
Primary outcome (both trials): change in ESS between baseline and end of treatment

*Trials excluded people with co-existing narcolepsy, psychiatric illness, cardiovascular system abnormalities, and severe co-morbidities

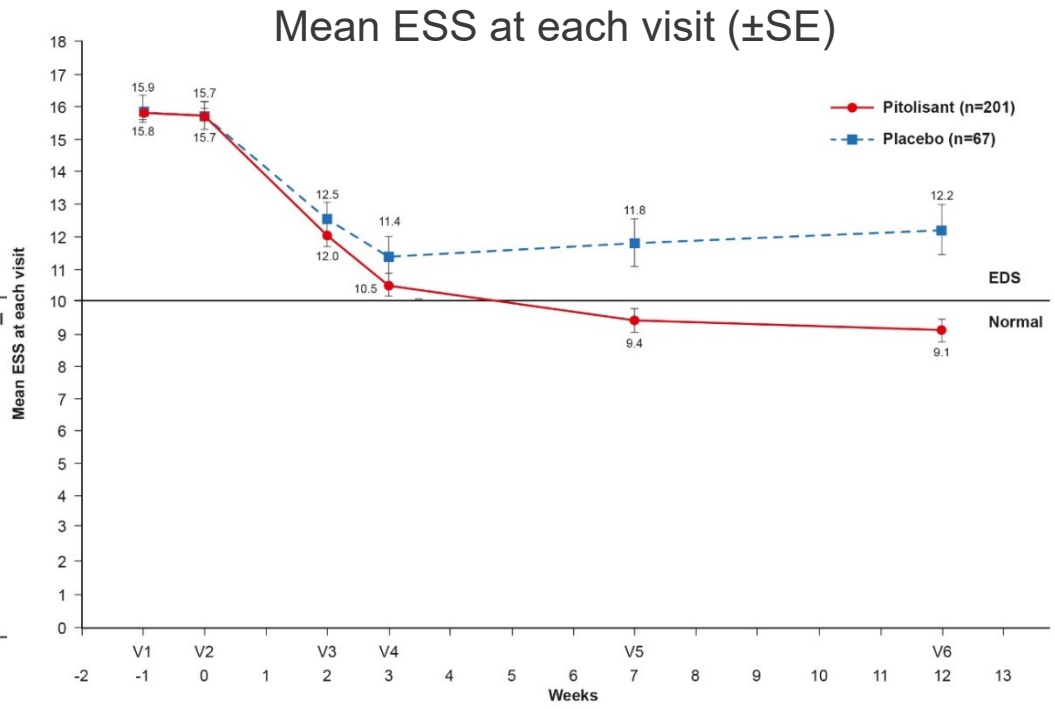
CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale

HAROSA I & II, 12 week results

HAROSA I (previous CPAP use)



HAROSA II (refused CPAP)



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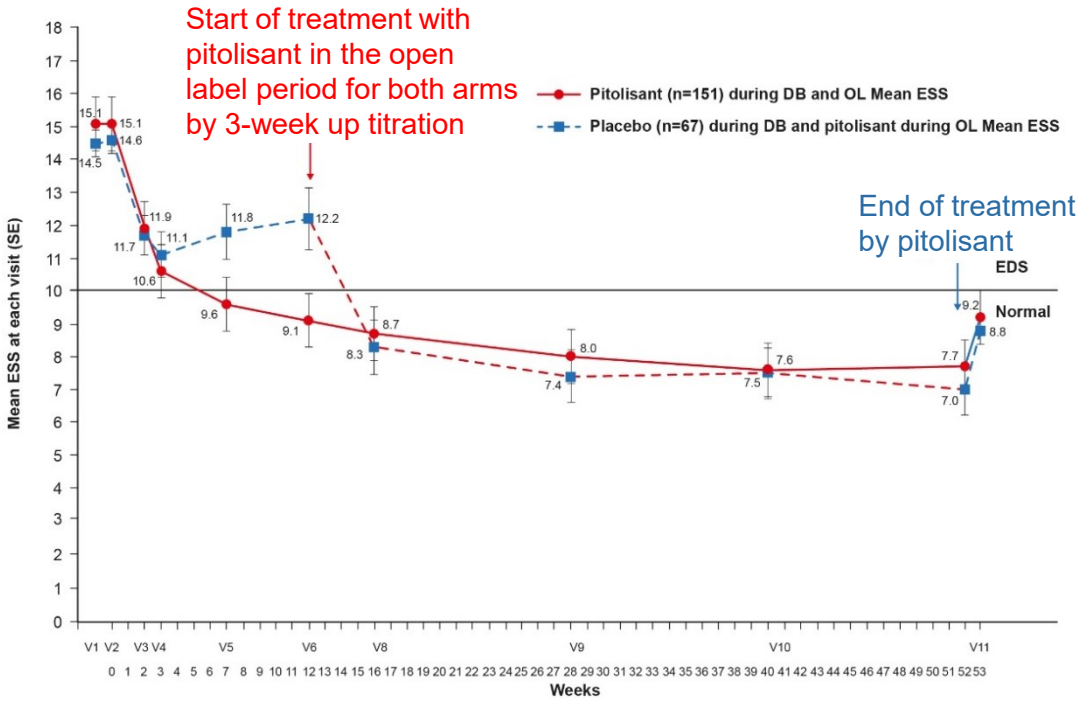
CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; SE, standard error

HAROSA I & II, overall results

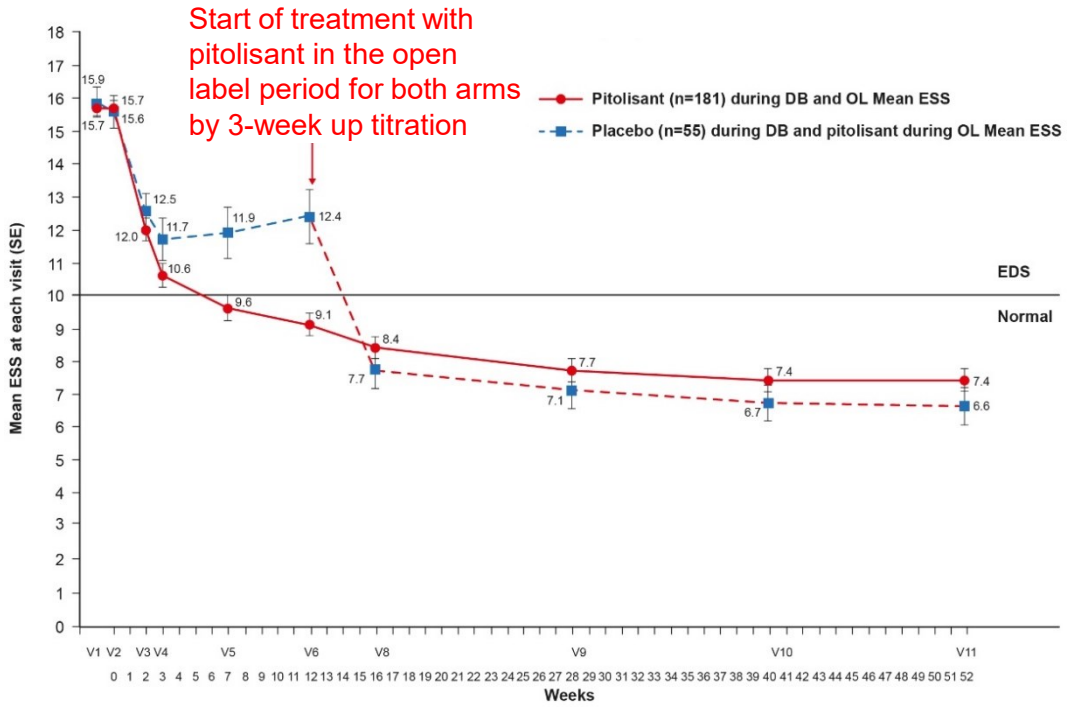
HAROSA I (previous CPAP use)

Mean ESS at each visit (±SE)



HAROSA II (refused CPAP)

Mean ESS at each visit (±SE)



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CPAP, continuous positive airway pressure; DB, double blind; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OL, open label; SE, standard error

HAROSA I & II key results

Mean ESS & SD during 12 week double blind period

	Treatment	Baseline	12 weeks, LOCF	Difference	
HAROSA I	Pitolisant	14.9 (2.7)	9.42 (4.7)	-5.52 (4.4)	Mean difference: 2.77 **Treatment effect: -2.6 (95% CI -3.9 to -1.4) (p<0.001)**
	Placebo	14.6 (2.8)	11.87 (5.7)	-2.75 (5.9)	
HAROSA II	Pitolisant	15.7 (3.1)	9.4 (4.6)	-6.3 (4.5)	Mean difference: 2.7 **Treatment effect: -2.8 (95% CI -4.0 to -1.5) (p<0.001)**
	Placebo	15.7 (3.6)	12.1 (5.8)	-3.6 (5.5)	

Mean ESS & SD during 40 week open label period

	Treatments	Entry into open label	40 weeks, LOCF	Difference
HAROSA I	Pitolisant, pitolisant	9.4 (4.8)	8.1 (4.7)	-1.21 (3.1)
	Placebo, pitolisant	12.0 (6.0)	7.9 (5.1)	-4.07 (5.3)
HAROSA II	Pitolisant, pitolisant	9.3 (4.6)	7.7 (4.5)	-1.6 (3.4)
	Placebo, pitolisant	12.2 (5.6)	7.0 (4.0)	-5.2 (5.4)

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CI, confidence interval; ESS, Epworth Sleepiness Scale; LOCF, last observation carried forward; SD, standard deviation

Committee's considerations in ACD

Key issue	Committee's conclusion	
Placebo effect (ACD 3.6, 3.14)	Appropriate to explore placebo adjustments	
HAROSA trials generalisability (ACD 3.7)	HAROSA trials broadly generalisable	
CPAP adherence (ACD 3.8)	CPAP use unlikely to be affected by pitolisant treatment because of regular monitoring	
Comparison with mandibular advancement devices (ACD 3.9)	Acceptable to exclude mandibular advancement devices given limited data	
Trial follow up (ACD 3.10)	Follow-up period sufficiently long	
Treatment impact on cardiovascular events (ACD 3.13)	No direct clinical evidence for pitolisant impact on cardiovascular events	
Utility values (ACD 3.15)	Preferred to see trial EQ-5D utility values & more evidence to justify its insensitivity	
Road traffic accident utility decrement (ACD 3.16)	No utility decrement for road traffic accidents	

Resolved Partially resolved Unresolved

ACD, appraisal consultation document; CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale

ACD consultation comments

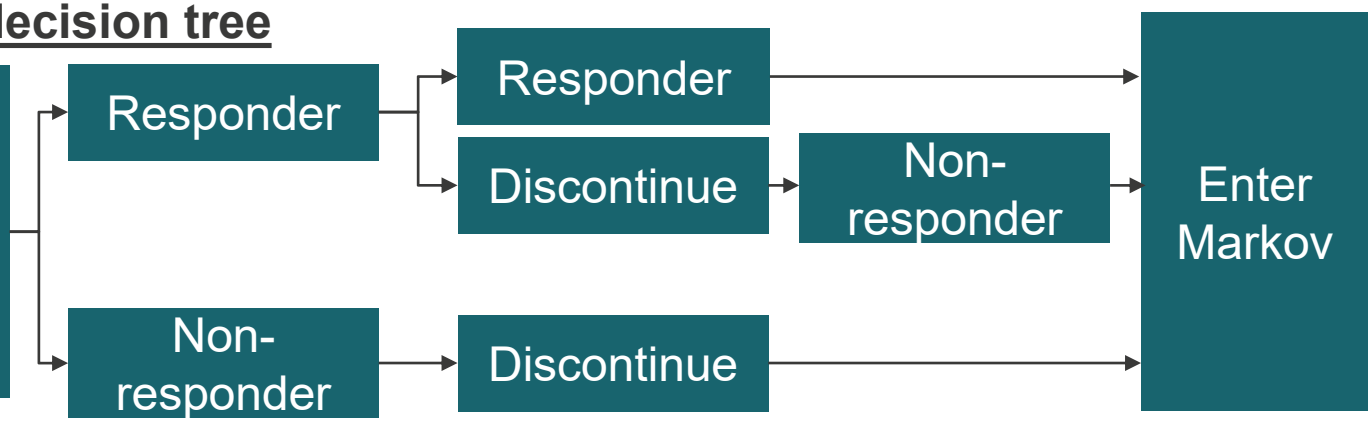
- Comments received from
  - Clinical expert
  - Patient expert
  - Bioprojet UK (company)
  - Jazz Pharmaceuticals (solriamfetol company)

Company's ACD model

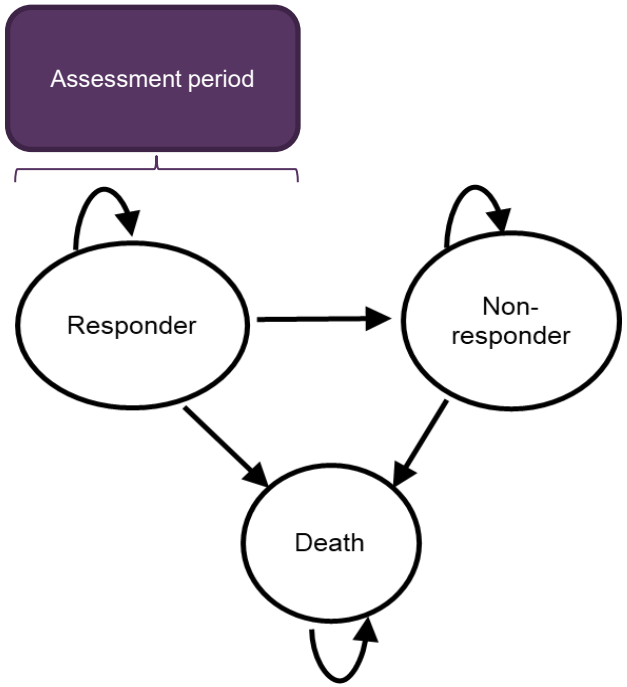
First 52 weeks of treatment: decision tree

People with OSA and ESS >10 having:

- Pitolisant + CPAP + BSC
- CPAP + BSC
- Pitolisant + BSC
- BSC alone



Week 52 onwards: Markov model



Company's ACD response

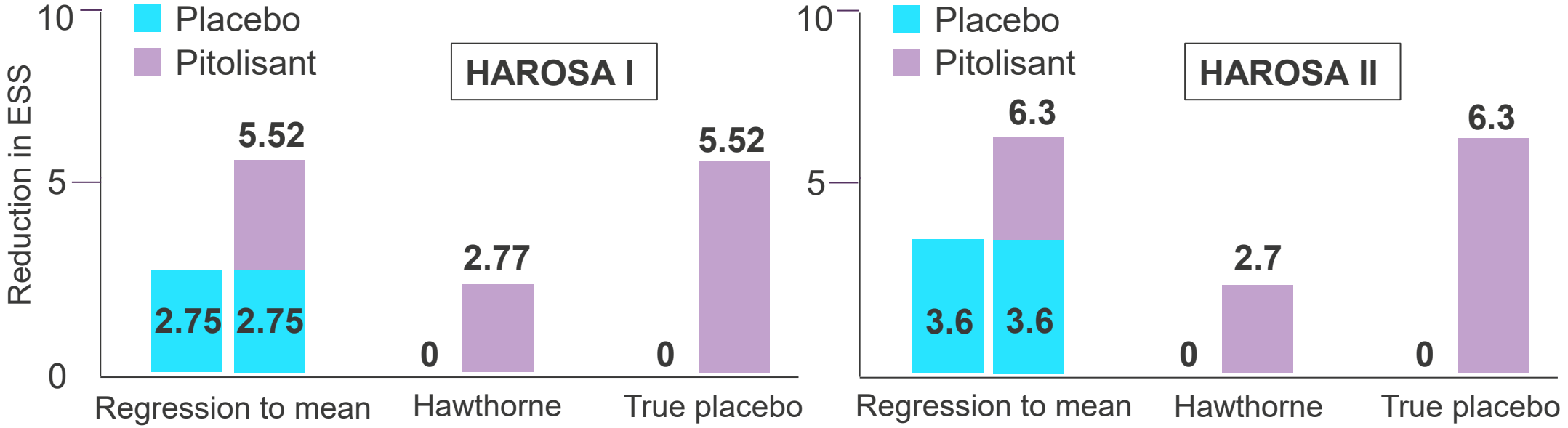
- Placebo centering: subtracted mean change in ESS on BSC from change in ESS for each patient
- Differences from ID1499 solriamfetol model:
  - 2-point ESS change for treatment response (in line with ERG comments on ID1499 model)
  - Placebo treated patients can be 'responders'
  - McDaid utility mapping (same as original pitolisant model)
- Road traffic accidents & impact of treatment on cardiovascular events not included

ACD, appraisal consultation document; BSC, best supportive care; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea

Issue 1: Placebo effect (1/2)

Issue background (ACD 3.6, 3.14)

- Epworth Sleepiness Scale (ESS) improved by week 12 in **placebo** in HAROSA trials
  → Original pitolisant model did not adjust for placebo effect
- ID1499 solriamfetol explored Hawthorne effect, regression to the mean, and true placebo
- Committee concluded it was appropriate to explore adjustments



Regression to mean

- Tendency for extreme values to return to average
- Same response would be observed in routine practice without the placebo
- Do not adjust trial data

Hawthorne effect

- Due to being observed in trial
- Assumes no response to placebo in routine practice
- Placebo response subtracted from pitolisant
- Adjustment called ‘centring’

True placebo

- Placebo response would be seen irrespective of setting
- Response to active treatment / placebo will be same as in trial
- If placebo not administered, no response in routine practice

Issue 1: Placebo effect (2/2)

Company's ACD response

- New model with placebo centring approach, adjusting for **Hawthorne effect**
- Centred mean ESS scores pooled from HAROSA I & II
- Baseline ESS: HAROSA I, 11.9 & HAROSA II, 12.1

	Pooled mean ESS* (SD)
Responders	
BSC	8.42 (± 4.13)
Pitolisant	7.76 (± 3.46)
Total	7.88 (± 3.60)
Non-responders	
BSC	16.40 (± 4.06)
Pitolisant	15.20 (± 3.43)
Total	15.68 (± 3.73)

*centred value

	Treatment arm	Mean ΔESS from baseline*
HAROSA I		
Responder	Pitolisant + CPAP + BSC	-4.11
	CPAP + BSC	-3.45
Non-responder	Pitolisant + CPAP + BSC	4.53
	CPAP + BSC	3.33
HAROSA II		
Responder	Pitolisant + BSC	-4.34
	BSC	-3.68
Non-responder	Pitolisant + BSC	3.10
	BSC	4.30

ERG critique

In line with ACD comments for responder/non-responder status and placebo adjustment

Have the placebo adjustments been sufficiently explored?

ACD, appraisal consultation document; BSC, best supportive care; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; SD, standard deviation; Δ, change

Issue 2: Utility values (1/2)

Issue background (ACD 3.15)

- EQ-5D showed no difference between pitolisant & placebo → company noted EQ-5D may not capture QoL benefits for people with OSA
- Company's base case mapped ESS to EQ-5D using McDaid approach from TA139 CPAP
  - Provided scenario using mapped SF-6D
- Committee preferred trial EQ-5D and additional justification for its insensitivity

Company's ACD response

- ACD model: McDaid mapping ESS to EQ-5D
- Did not include NHWS mapping because some baseline covariate values not available and would make comparison with original model difficult
- Explored EQ-5D insensitivity by considering 3 metrics: EQ-INDEX, EQ-VAS, Z-score
  - EQ-INDEX shows no significant difference between pitolisant & placebo
  - EQ-VAS & Z-score show pitolisant benefit but don't equate to utility values
  - Concluded mapping from ESS most appropriate

	Baseline utility
HAROSA I	0.766
HAROSA II	0.737

Company mapped utility values*		
	HAROSA I	**HAROSA II**
BSC		
Responder	0.926	0.928
Non-responder	0.849	0.851
Pitolisant		
Responder	0.932	0.935
Non-responder	0.860	0.862

*from extended ACD response document, different than values in model

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ACD, appraisal consultation document; BSC, best supportive care; CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; NHWS, National Health and Wellness Survey; OSA, obstructive sleep apnoea; SF-6D, short-form six-dimensions; QoL, quality of life; VAS, visual analogue scale;

Issue 2: Utility values (2/2)

ERG critique of company's ACD response

- Unclear how baseline trial utility values are derived
- Mapped utility values appear high due to error, corrected values in table below
  → Company: *(change ESS*ESS coefficient) + (baseline utility*baseline ESS) + constant*
  → McDaid approach: *(change ESS*ESS coefficient) + baseline utility*
- Company's analysis of EQ-5D INDEX refers to EQ-5D sum-score that was standardised and reversed to 0-100 → results **do not** provide evidence that EQ-5D utility is insensitive
- EQ-VAS suggests benefits to perceived QoL, but different concept than EQ-5D utilities
- ACD comment that if EQ-5D does not capture QoL benefits adequately, results should not be mapped to EQ-5D because it will remain insensitive

ERG mapped utility values

	HAROSA I	HAROSA II
BSC		
Responder	0.799	0.773
Non-responder	0.722	0.695
Pitolisant		
Responder	0.806	0.779
Non-responder	0.734	0.707

EQ-5D mean utility difference: baseline to end of double blind phase (95%CI)

	HAROSA I	HAROSA II
Pitolisant	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

Solraimfetol company ACD response

NHWS mapping algorithm developed by Jazz Pharmaceuticals should be explored

Are the ESS mapped to EQ-5D using McDaid utility values appropriate?

ACD, appraisal consultation document; BSC, best supportive care; CI, confidence interval; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; NHWS, National Health and Wellness Survey; QoL, quality of life; VAS, visual analogue scale

Issue 3: ACD model issues

ERG critique of company's ACD model

- No probabilistic sensitivity analysis → unknown probability pitolisant being cost effective
- Inconsistency in modelled 12-week assessment period, prefer both treatment arms assigned baseline utility, rather than responder/non-responder utility
- Transition probabilities from 12 weeks for responder/non-responders calculated from number of people in each arm still on treatment during open label phase
  - → Unclear if discontinuation rate can be used to estimate rate of losing treatment response and no justification is provided
  - → HAROSA I, week 12: 151 people on pitolisant, but 104 classed as responders
  - → Open-label phase used to estimate transition probability from responder to non-responder for BSC, but people had pitolisant in open-label period so not appropriate
- Noted errors in Markov trace sheets referring to lower limit of CI not mean utility
- Model does not include people on 10 mg dose or wastage (previous model did)

Solriamfetol company ACD response – comments on original model

- Impact of pitolisant on resource use has not been adequately considered
- Pitolisant is positioned as an add-on to primary therapy, so both the direct cost and the cost related to disutility of hospitalisation could create uncertainty around the true ICER
- Urge the committee to consider OSA specific hospitalisation data

Is the company's updated model appropriate for decision making?

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ACD, appraisal consultation document; BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; OSA, obstructive sleep apnoea

Issue 4: Adherence to CPAP

Issue background (ACD 3.8)

- Patient expert explained some people may prefer to manage symptoms with medicine rather than using CPAP
- Committee concluded pitolisant treatment unlikely to impact CPAP use because of monitoring

Patient expert ACD comments

If pitolisant were to be approved, it should be on the basis that CPAP use must be regularly monitored until the sleep clinic is satisfied that the patient will continue combined therapy

Solraimfetol company ACD response

- CPAP use unlikely to be affected by other treatments, but evidence not fully explored
- HAROSA I measured nightly CPAP adherence, but evidence not presented
- OSA symptom control has been linked to CPAP adherent use
- Clinician and patient experts raised the concern of introducing a pharmacotherapy potentially influencing adherence with CPAP in ID1065 and ID1499
- Considerable clinical and health economic uncertainty on this issue

Is the evidence presented for impact of pitolisant treatment on CPAP adherence sufficient?

ACD, appraisal consultation document; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea

Other considerations

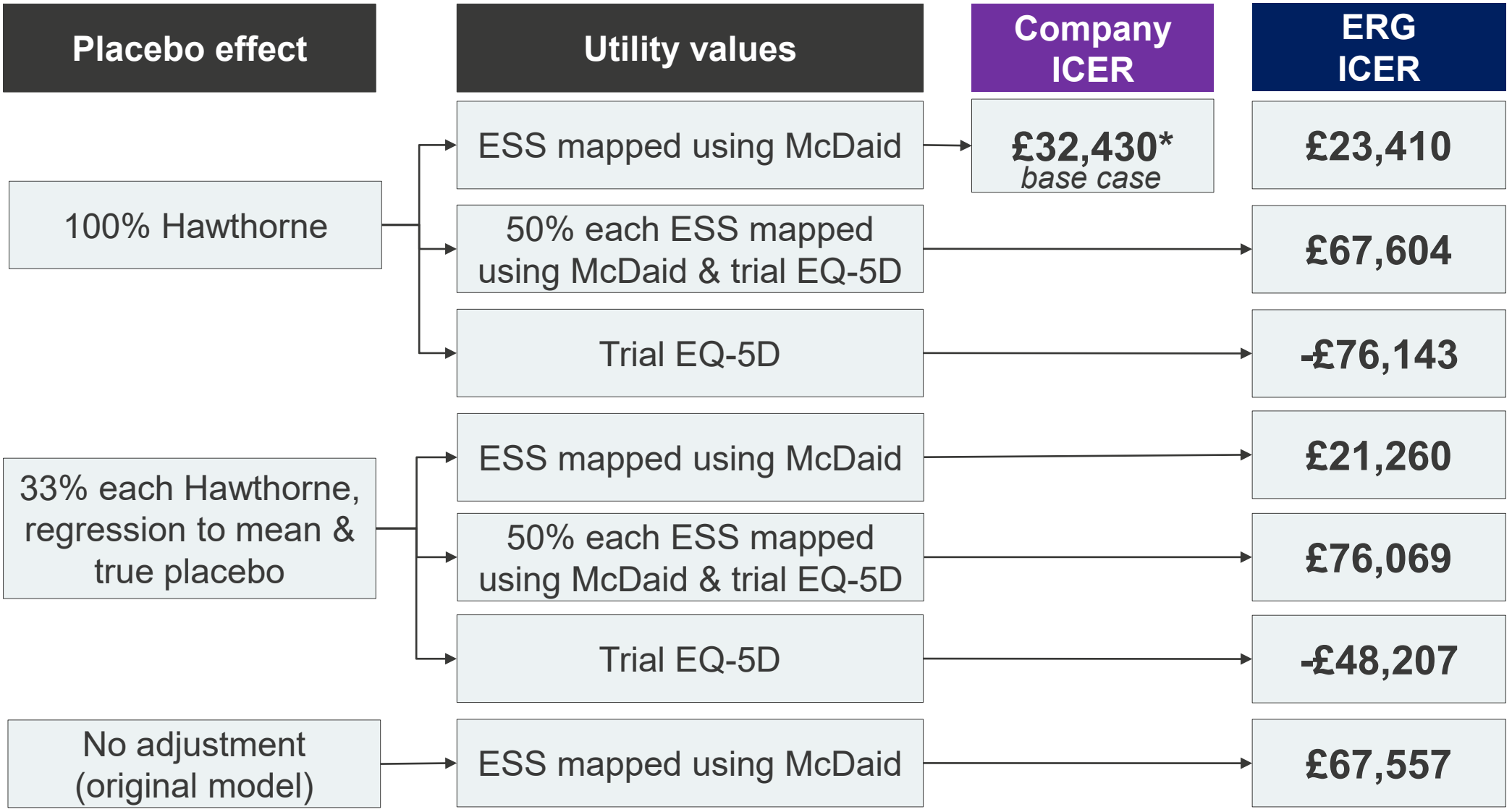
Innovation

- Clinical experts: Pitolisant is innovative as no current treatment in this area so could have substantial benefit (which needs to be offset with the substantial infrastructure improvement needed). *Noted at first committee meeting*

Equality issues

- People with neurodegenerative conditions or mental health issues with residual excessive daytime sleepiness could be discriminated against if the recommendations restricted pitolisant for use with CPAP only. *Noted at first committee meeting*

Deterministic cost-effectiveness results for add on to CPAP population, HAROSA I (pitolisant list price)

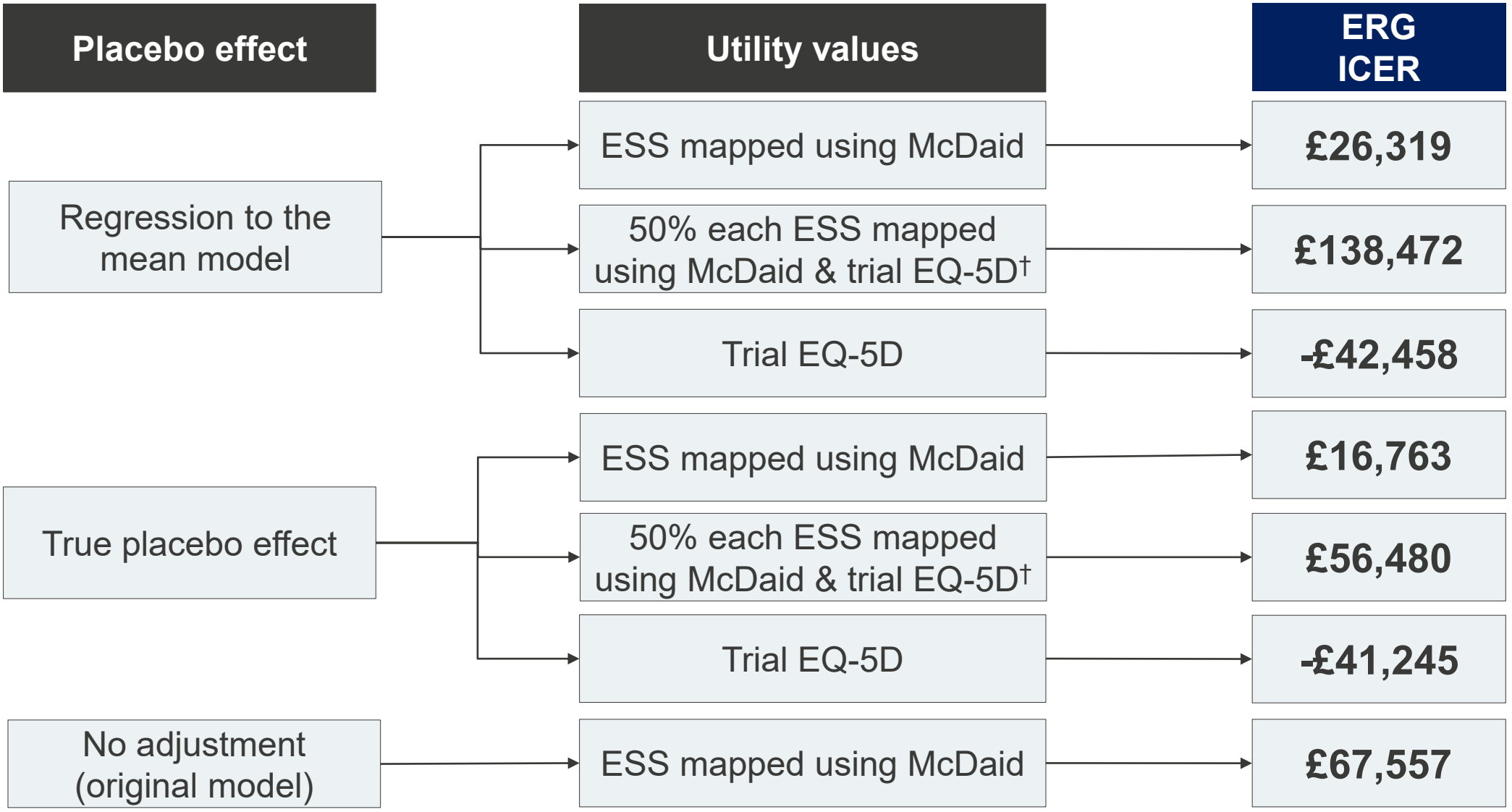


Trial EQ-5D utility values had UK (Dolan) tariff applied

*25 year time horizon
† Average of utility values

CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio

Deterministic cost-effectiveness results for add on to CPAP population, HAROSA I (pitolisant list price)



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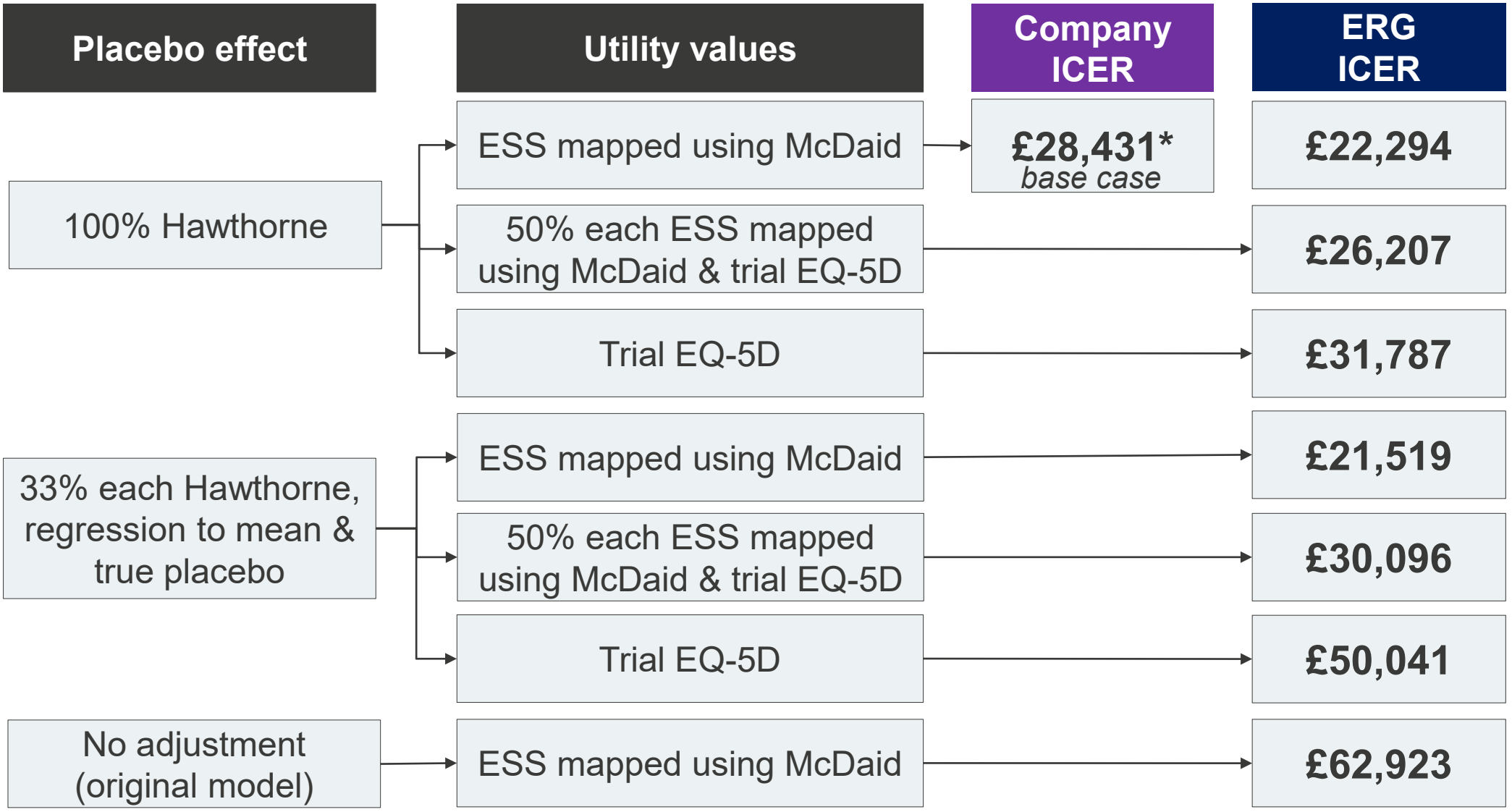
CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio

Deterministic cost-effectiveness results for CPAP non-users, HAROSA II (pitolisant list price)



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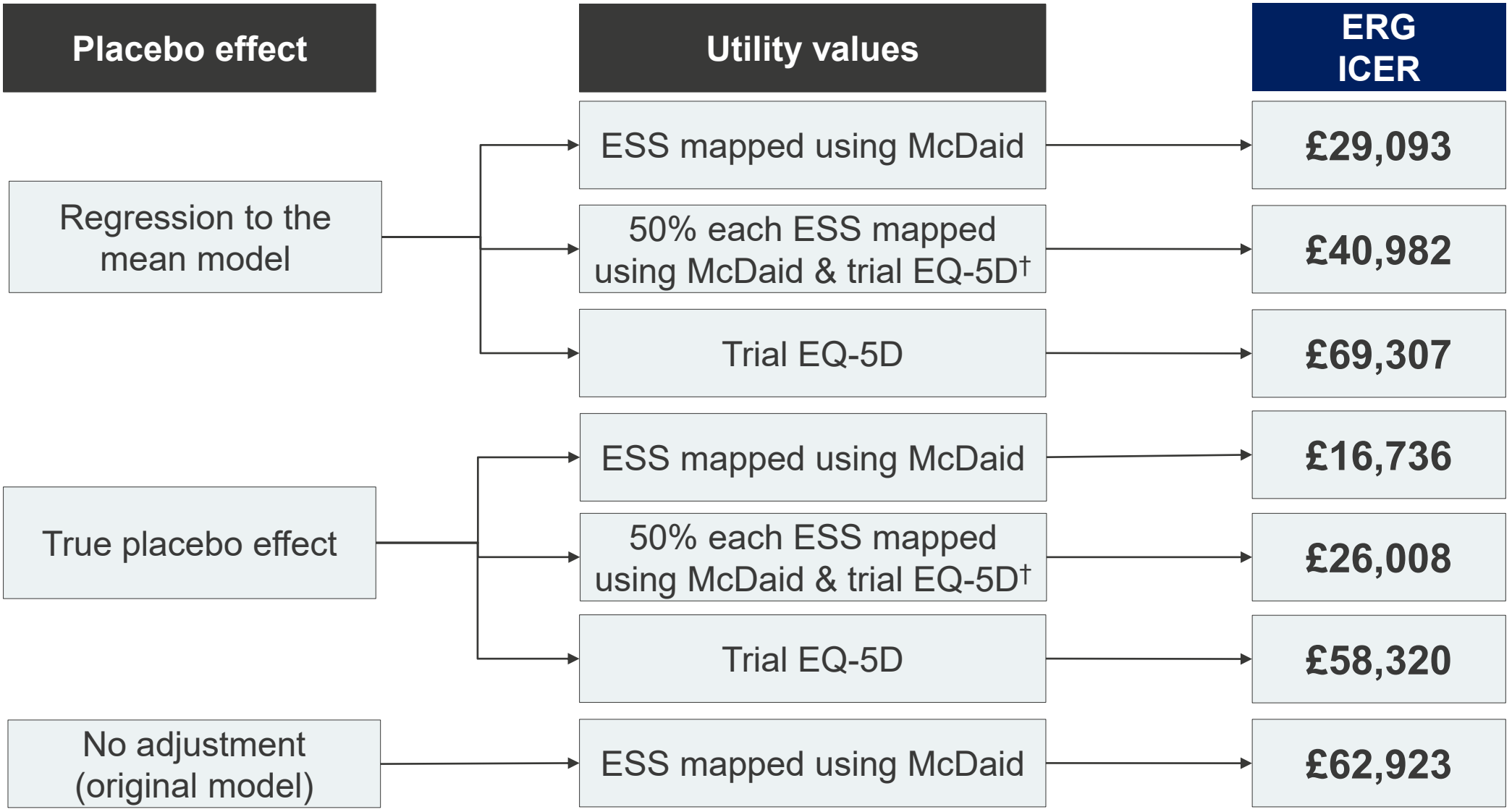

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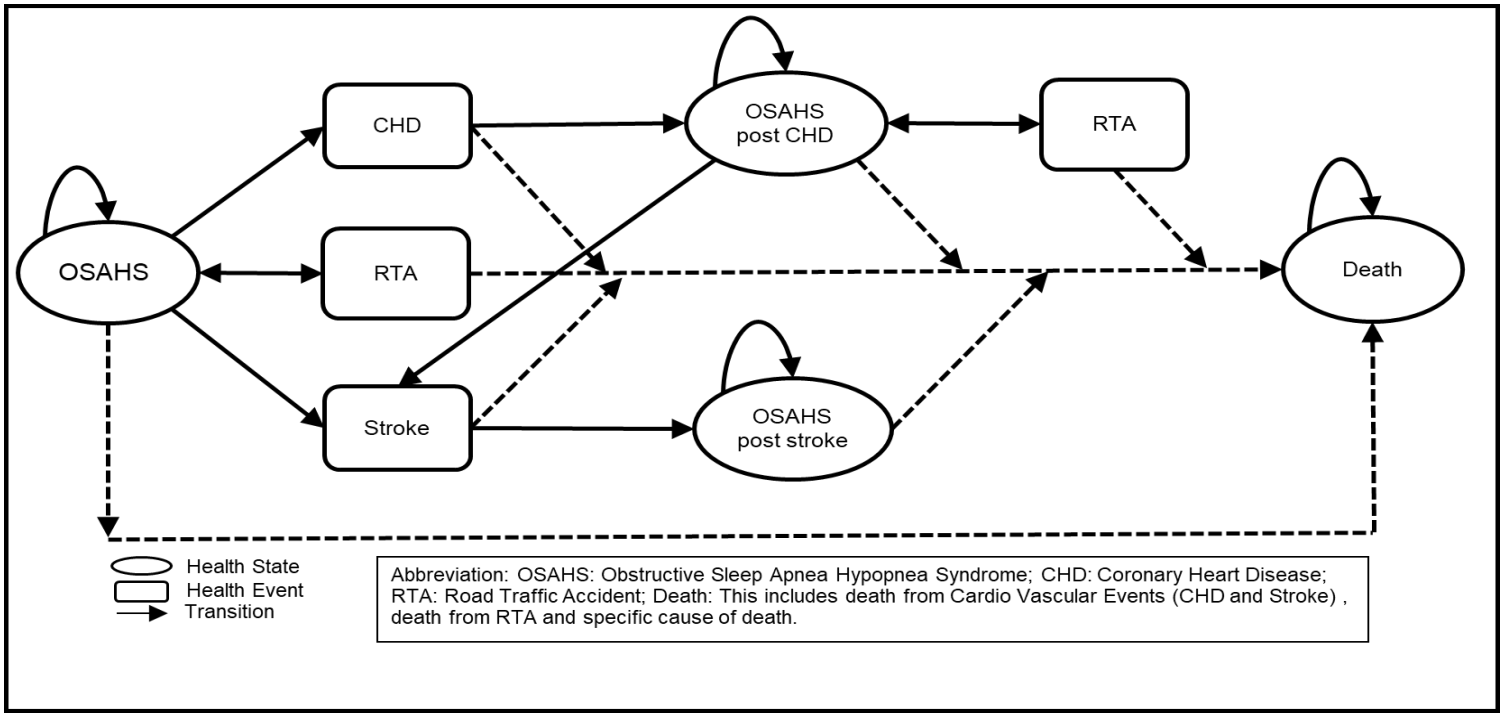
† Average of utility values

CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio

Company's original model

Model characteristics

- Cohort-level state transition model
- 4 health states
- Annual cycle length
- Time horizon 25 years (revised at clarification)
- Costs, benefits discounted at 3.5% pa



Input	Data source
Clinical data	• HAROSA I (previous CPAP) & II (refused CPAP)
Treatment waning effect	• Lifetime effect • Assumed patients are on pitolisant for the rest of their life
Utilities	• Algorithm that allows mapping ESS to EQ-5D
Costs	• Lincoln Pharmaceutical pitolisant price • PSSRU 2019

CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; EQ-5D, EuroQol five-dimensions; PSSRU, Personal Social Services Research Unit

Issue 2: Utility values

Company mapped EQ-5D utility values from ACD model		
	HAROSA I	HAROSA II
BSC		
Responder	0.928	0.930
Non-responder	0.851	0.853
Pitolisant		
Responder	0.935	0.937
Non-responder	0.862	0.862

	Mapped SF-6D mean utility values (scenario in original model)			
	Treatment	OSAHS	Post stroke	Post CHD
HAROSA I	**Pitolisant**	0.718	0.666	0.677
	BSC	0.694	0.641	0.653
HAROSA II	**Pitolisant**	0.716	0.664	0.675
	BSC	0.692	0.639	0.650

ACD, appraisal consultation document; BSC, best supportive care; CHD, coronary heart disease; EQ-5D, EuroQol five-dimensions; OSAHS, obstructive sleep apnoea hypopnoea syndrome; SF-6D, short-form six-dimensions