NICE National Institute for Health and Care Excellence

Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1499]

Chair's presentation

2nd Appraisal Committee Meeting

Chair: Stephen O'Brien

ERG: Southampton Health Technology Assessment Centre

Technical team: Nigel Gumbleton, Charlie Hewitt, Jasdeep Hayre

Company: Jazz Pharmaceuticals

14th September 2021

Solriamfetol not recommended

Why the committee made these recommendations

- Uncertainty in the adjustment for placebo effect
- Changes in quality of life may not have been adequately captured by mapping the ESS to the EQ-5D
- No evidence of clinical and cost-effectiveness of solriamfetol without standard care presented, therefore the evidence submitted by the company does not cover the full marketing authorisation
- Unclear whether adherence to primary OSA therapy would be reduced with the addition of solriamfetol
- The modelling did not include hospitalisation costs

ESS: Epworth sleepiness scale; OSA: obstructive sleep apnoea

Key issues for consideration

1. Placebo effect	How much of placebo response in TONES 3 was due to: 1) True placebo; 2) Hawthorne effect; 3) Regression to mean?
2. Utilities	Which utilities are most appropriate/plausible?
3. People who cannot tolerate CPAP	Are analyses of solriamfetol alone compared with standard care appropriate for decision making in people who cannot tolerate CPAP?
4. Adherence to primary OSA therapy	Is adherence to primary OSA therapy likely to be affected by solriamfetol treatment?
5. Hospitalisation costs	What hospitalisation rates are most appropriate to use in the model?
6. Partner utility values	Should partner utilities be included in the analysis?
7. Dose split assumption	What is the most appropriate dose-split assumption?
8. Prescribing setting	Will solriamfetol be restricted to secondary care only prescribing?

CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea

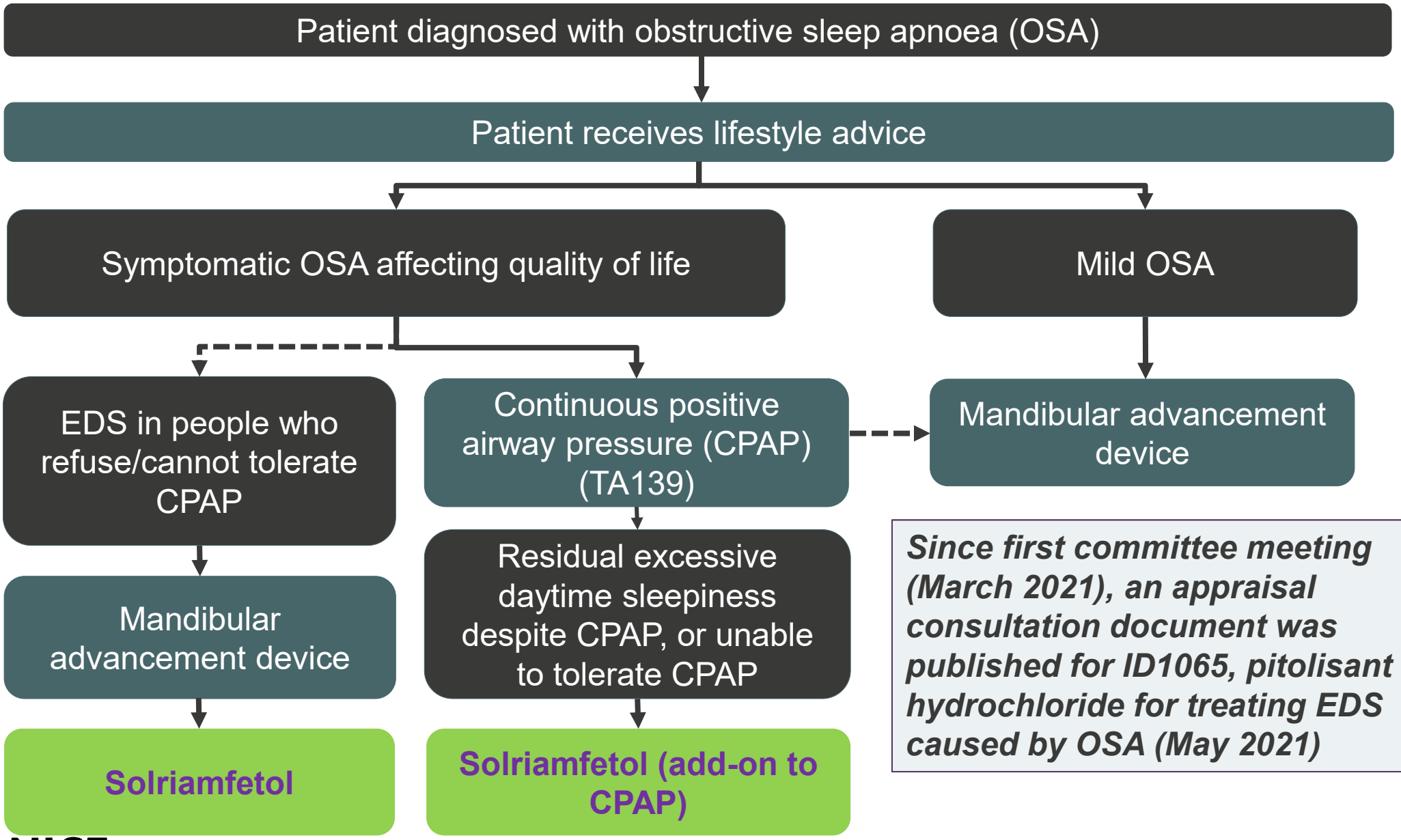
Solriamfetol (Sunosi, Jazz Pharmaceuticals)

Mechanism of action	Derivative of the amino acid phenylalanine. Mechanism of action yet to be fully characterised, thought to be through activity as dopamine and noradrenaline reuptake inhibitor
Marketing authorisation	Indicated to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure
Dosage and Administration	• Tablet, 37.5 mg, 75 mg or 150 mg once daily • Recommended starting dose is 37.5 mg once daily, upon awakening. Depending on clinical response, dose can be titrated to a higher level by doubling the dose at intervals of at least 3 days, with a recommended maximum daily dose of 150 mg
List Price*	• £177.52 per pack of 28 x 75 mg film-coated tablets • £248.64 per pack of 28 x 150 mg film-coated tablets • Minimum cost per year at list price is £1,154 • Maximum cost per year at list price is £3,241

*Jazz Pharmaceuticals has agreed a PAS discount with NHS England for solriamfetol

PAS: patient access scheme

Treatment pathway – current and proposed



Since first committee meeting (March 2021), an appraisal consultation document was published for ID1065, pitolisant hydrochloride for treating EDS caused by OSA (May 2021)

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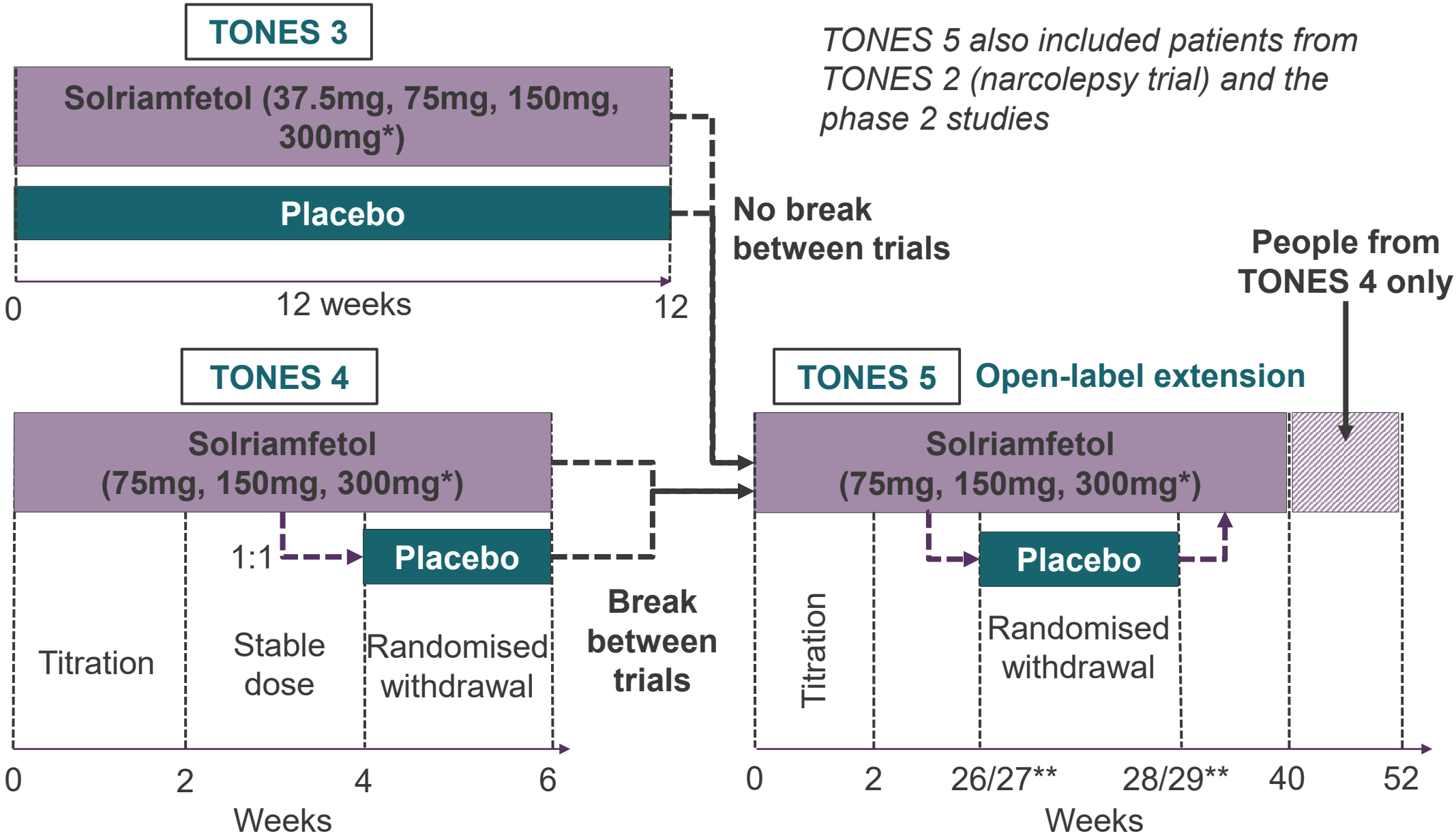
EDS: excessive daytime sleepiness

Overview of solriamfetol trial programme



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* Dose not included in marketing authorisation

** Weeks 26 to 28 for people from TONES 4; weeks 27 to 29 for people from TONES 3

Key clinical trial results

TONES 3 results (adults with OSA and a baseline ESS score of 10 or more)

12-week results (modified ITT population)	Placebo (n=114)	Solriamfetol		
		37.5 mg (n=56)	75 mg (n=58)	150 mg (n=116)
Change in ESS score from baseline, LS mean (standard error [SE])	-3.3 [redacted]	-5.1 [redacted]	-5.0 [redacted]	-7.7 [redacted]
p value	-	0.0161	0.0233	<0.0001
Change in MWT from baseline, LS mean (SE)	0.2 [redacted]	4.7 [redacted]	9.1 [redacted]	11.0 [redacted]
p value	-	0.0086	<0.0001	<0.0001
AEs leading to discontinuation, n (%)	4 (3.4)	3 (5.2)	2 (3.2)	5 (4.3)

TONES 5 results (patients with OSA for 75 mg and 150 mg doses [Safety population])

Change in mean ESS score from baseline (SD)	Group A (from TONES 3)		Group B (from TONES 4)	
	75 mg [redacted]	150 mg [redacted]	75 mg [redacted]	150 mg [redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	NA	NA
Week 52	N/A	N/A	[redacted]	[redacted]

For Group A, baseline from parent study. For Group B, baseline from TONES 5

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AEs: adverse events; ESS: Epworth sleepiness scale; LS: least squares; ITT: intention-to-treat; MWT: maintenance of wakefulness test; OSA: obstructive sleep apnoea; SD: standard deviation

Committee's considerations in ACD

Issue (ACD section)	Committee judgement in ACD	Provided	Included in base case
Placebo effect (3.9)	Wanted threshold analysis with regression to mean effect	✓	N/A
Utility values (3.11)	Wanted analysis with SF-6D data	✗	✗
People who cannot tolerate CPAP (3.7)	Wanted clinical/cost-effectiveness results for people who cannot tolerate CPAP	✓	N/A
Adherence to primary OSA therapy (3.6)	More data needed whether solriamfetol affects adherence to CPAP	✓	N/A
Hospitalisation costs (3.13)	Include costs for serious adverse events	✓	✓
Partner utility values (3.12)	Important to consider but not enough evidence to support inclusion	✓	✗
Dose splits (3.14)	Dose split assumptions are appropriate	✓	✓
Prescribing setting (3.4)	Likely limited to secondary care, more information needed	✓	N/A
Treatment response (3.8)	Define as ESS score reduced by 2 or more	✓	✓
Discontinuation and loss of response rates (N/A*)	Dose dependent	✓	✓

NICE * Issue 7 from 1st committee meeting slides

CPAP: continuous positive airway pressure; ESS: Epworth sleepiness scale; OSA: obstructive sleep apnoea

ACD consultation comments

- Comments received from:
  - Jazz pharmaceuticals (company)
  - British Thoracic Society
  - Member of the public with obstructive sleep apnoea

Consultation comments summary

Public comments

- Other than CPAP there is nothing that the NHS can offer for people with EDS caused by OSA
- OSA is linked to many adverse impacts for individuals - for example, many people struggle to exercise regularly due to fatigue which may lead to other health issues, therefore incurring a cost to the NHS to treat those issues

British Thoracic Society

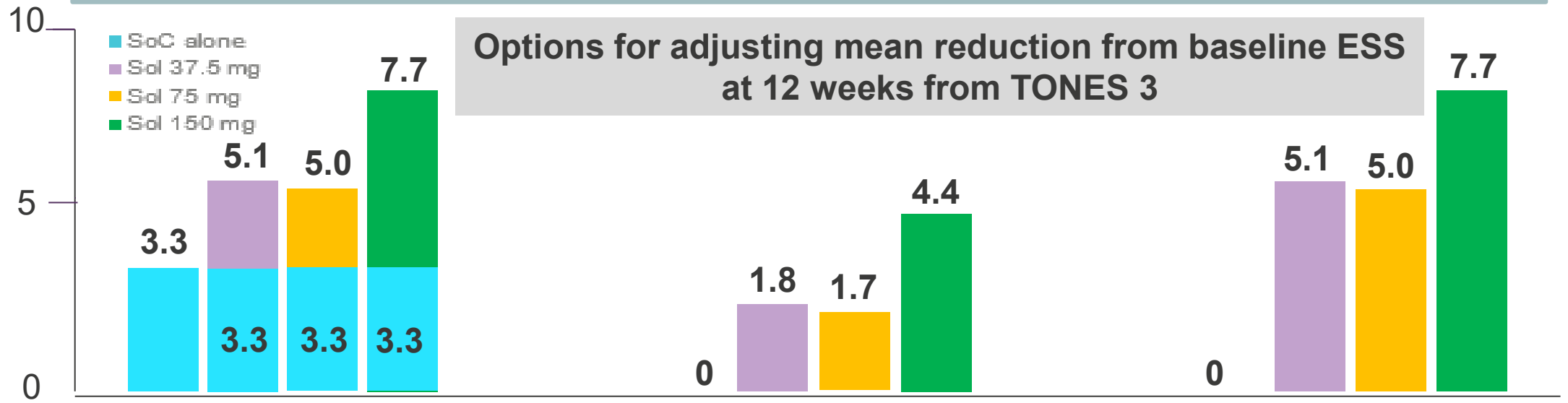
- The provisional recommendations are appropriate

CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; OSA: obstructive sleep apnoea

1. Placebo effect: background

- In TONES 3 a reduction in Epworth sleepiness scale (ESS) score of 3.3 observed in placebo arm. Company used centring approach, all on standard care remain at baseline ESS
- Company adjusted the change from baseline to week 12 in the solriamfetol arms by the mean observed change from baseline to week 12 in the placebo arm

Committee: company's adjustment method plausible but may be some regression to mean. Wanted threshold analysis assuming regression to mean, or external data on ESS variations



Regression to mean (ERG)

- 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 (company)

- Placebo response due to being observed in trial
- Assumes no response to placebo in routine practice
- Placebo response subtracted from solriamfetol

True placebo (sensitivity analysis)

- 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

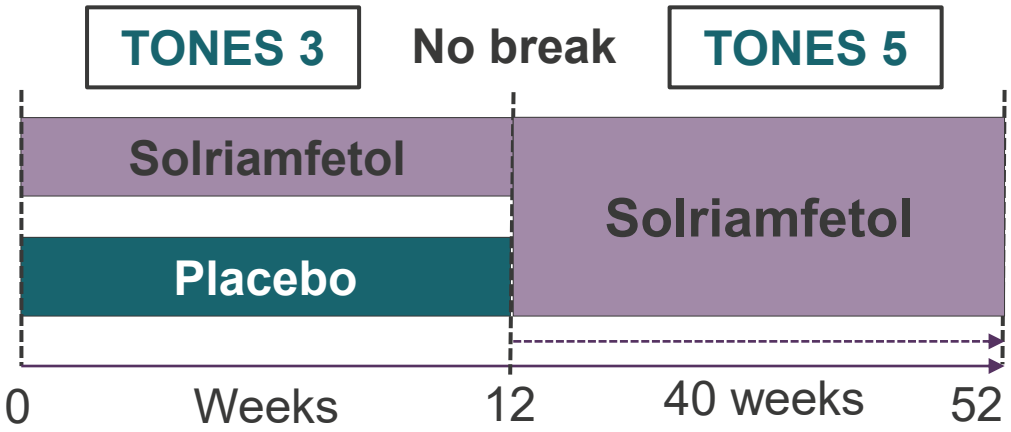
1. Placebo effect: company response [1]

Company's consultation comments

- Revised base-case conservatively maintains placebo effect was due to Hawthorne effect. However, company believes it is primarily a true placebo effect
- Explored regression to mean by removing centring exercise and responder/non-responder split; considers SoC without solriamfetol arm as single group
  - For non-responders to SoC plus solriamfetol at week 12, ESS changes to that of the SoC without solriamfetol group, [redacted], reflecting regressed mean position
- Provided evidence that placebo effect is not regression to the mean:
  - TONES 3 – onset of placebo effect (1 week) too rapid for regression to mean
  - Similar speed of ESS reduction in TONES 3, 4 and 5 for people starting solriamfetol, and for people restarting solriamfetol in TONES 5
  - TONES 4 – those continuing solriamfetol during randomised withdrawal phase did not have increase in ESS score, unlike those having placebo
  - TONES 5 – where measured, ESS scores at screening and baseline were stable

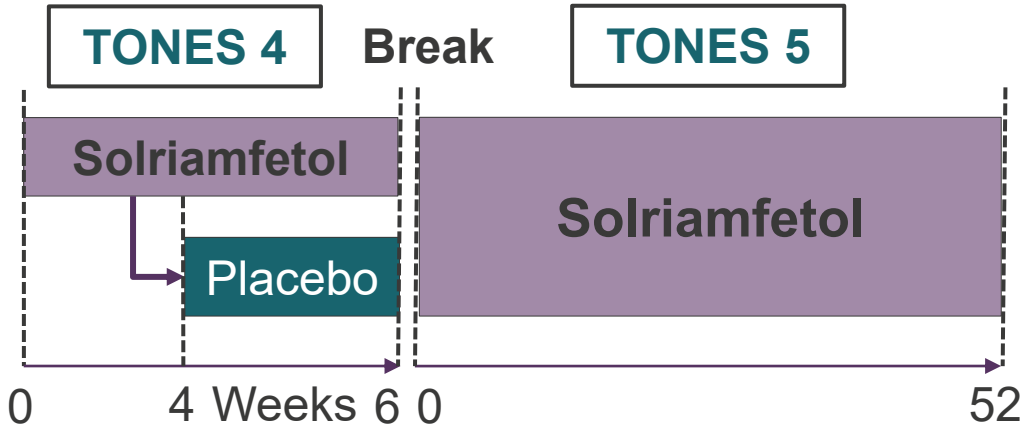
ESS: Epworth sleepiness scale; SoC: standard of care

1. Placebo effect: company evidence against RTM



[redacted]

- ESS scores decreased rapidly in TONES 5 for placebo group from TONES 3
- Improvement in ESS at similar rate in placebo and solriamfetol arms



[redacted]

- During RW placebo group had ESS increase
- TONES 4 and 5 baseline ESS scores: [redacted]. Indicates neither was extreme
- Speed of ESS decrease similar in TONES 4/5

ESS: Epworth sleepiness scale; RTM: regression to the mean; RW: randomised withdrawal

1. Placebo effect: ERG comments [1]

ERG comments

- Removing SoC split, and ESS stable unless solriamfetol stopped: reasonable assumptions
- Company presents results over limited range of regression to mean contribution (0% to 33%). If contribution of regression to mean is ≥40%, ICER is >£20,000 per QALY
- Company assumes same ESS and utility in non-responders as SoC at 12 weeks. Trial data shows non-responders have lower mean ESS at 12 weeks than SoC
  - If [redacted] utility for non-responders used (rather than [redacted]), solriamfetol dominated by SoC
- Uncertainty in ERG version of regression to mean analysis (4-state model, which allows for possibility of improvement on SoC without solriamfetol). Due to uncertainty in rates of transition between 'responder' and 'non-responder' status, based on discontinuation rates
- Company's evidence that placebo effect is not regression to the mean is useful

⊙ *How much of the placebo response in TONES 3 was due to: 1) A true placebo effect; 2) the Hawthorne effect; 3) Regression to the mean?*

ESS: Epworth sleepiness scale; SoC: standard of care

2. Utilities: background

- EQ-5D-5L collected in TONES 3 → showed [redacted] between treatment arms
- Company base case used NHWS mapping to estimate EQ-5D from ESS scores. McDaid algorithm and time trade off utilities used as scenarios
- SF-36 also collected in TONES 3, from which SF-6D can be derived → has greater sensitivity than EQ-5D in OSA

EQ-5D-5L index change from baseline in TONES 3	Placebo	Solriamfetol 37.5mg	Solriamfetol 75mg	Solriamfetol 150mg
LS mean change (standard error) LS mean diff vs placebo (p value)	0.02 (0.01)	0.01 (0.01) -0.01 ([redacted])	0.02 (0.01) 0 ([redacted])	0.03 (0.01) 0.01 ([redacted])
SF-36 change from baseline in TONES 3	**Placebo**	**Solriamfetol 37.5mg**	**Solriamfetol 75mg**	**Solriamfetol 150mg**
Physical: LS mean change (standard error) LS mean diff vs placebo (p value)	1.43 (0.61)	1.64 (0.88) [redacted]	1.99 (0.84) [redacted]	3.50 (0.60) 2.07 ([redacted])
Mental: LS mean change (standard error) LS mean diff vs placebo (p value)	1.05 (0.70)	2.65 (1.01) [redacted]	2.94 (0.97) [redacted]	3.10 (0.69) [redacted]

Committee: mapping from ESS to EQ-5D may not adequately capture changes in quality of life. Would like to see SF-6D in the analysis, which may be more sensitive

EDS: excessive daytime sleepiness; ESS: Epworth sleepiness scale; HRQoL: health-related quality of life; LS: least squares; OSA: obstructive sleep apnoea; NHWS: National Health and Wellness Survey; QoL: quality of life

2. Utilities: background and company response

Utility mapping methodology

NHWS mapping (company base case)	McDaid mapping (scenario)
Based on 2,348 adults across EU5 with OSA/narcolepsy, who completed the ESS	Based on individual patient data from 94 patients in the UK with OSA who completed the ESS and EQ-5D. Developed by ERG in NICE TA139
[redacted]	Simple linear regression model used to predict absolute utility scores from absolute ESS, controlling for baseline utility and baseline ESS

Company's consultation comments

- 12-week trial duration of TONES 3 insufficient to capture effect of disease on QoL
- Trial unlikely to reflect impact of improved EDS in UK, due to different driving restrictions
- EQ-5D/SF-36 data collected in TONES trials does not reflect burden of OSA on QoL
- Time trade off study represents real-world → suggests ICERs may be much lower
- Discussions with clinicians (narcolepsy specialists) suggest:
  - substantial QoL burden for people with EDS
  - shape of NHWS and McDaid graphs is appropriate
  - generic scales underestimate true burden of EDS on QoL

CPAP: continuous positive airway pressure; ESS: Epworth sleepiness scale; EDS: excessive daytime sleepiness; NHWS: National Health and Wellness Survey; QoL: quality of life; OSA: obstructive sleep apnoea

2. Utilities: overview of different approaches

Utility approach* and patient group		SoC	SoC plus solriamfetol		
			37.5 mg	75 mg	150 mg
Utilities from TONES 3 (EQ-5D index)	Baseline	[redacted]		[redacted]	
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]
NHWS mapping	Responder		[redacted]	[redacted]	[redacted]
	Non-responder year 1	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder year 2+			[redacted]	
McDaid algorithm	Responder		[redacted]	[redacted]	[redacted]
	Non-responder year 1	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder year 2+			[redacted]	
TTO study	Responder	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder year 1	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder year 2+			[redacted]	

* placebo effect attributed to Hawthorne effect

SoC: standard of care; TTO: time trade off

2. Utilities

ERG comments

- Direct estimates of utility from SF-6D would have provided useful additional evidence to supplement direct trial EQ-5D results and estimates from NHWS ESS to EQ-5D mapping
- McDaid ESS to EQ-5D mapped utilities company scenario is useful
- TTO utility estimates influenced by high emphasis on daytime sleepiness in health state descriptions. Unlikely to be comparable to EQ-5D-based utilities
- Company argues likely to take more than 12 weeks to achieve substantial change in SF-36. Not supported by TONES 5 QoL data, no further improvement over 40 weeks follow up
- If direct EQ-5D results from TONES 3 were used in the economic analysis, solriamfetol would not be cost-effective because EQ-5D utility results showed only small changes from baseline and no meaningful difference between the solriamfetol groups and placebo

⊙ *Which utilities are most appropriate/plausible?*

ESS: Epworth sleepiness scale; NHWS: National Health and Wellness Survey; TTO: time trade off; QoL: quality of life

3. People who cannot tolerate CPAP [1]

- Marketing authorisation allows solriamfetol to be offered alone or in combination with a primary obstructive sleep apnoea therapy
- Company positioned solriamfetol as an add-on to primary therapy, such as CPAP

Committee: evidence submitted does not cover full marketing authorisation. Wanted clinical and cost-effectiveness evidence for people not using a primary therapy

Company's consultation comments

- Individual patient data (IPD) from TONES 3: 26.5% of solriamfetol arm and 30.3% of placebo arm were not using primary OSA therapy at baseline
- IPD can be split into 2 groups: those using vs not using a primary OSA therapy at baseline
- Not a pre-specified analysis but presented summary data below and cost-effectiveness scenario analysis → solriamfetol cost-effective in both groups

	Responders (%)	Mean change in ESS from baseline	Responders (%)	Mean change in ESS from baseline
	Using primary OSA therapy		Not using primary OSA therapy	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]

CPAP: continuous positive airway pressure; ESS: Epworth sleepiness scale; OSA: obstructive sleep apnoea

3. People who cannot tolerate CPAP [2]

ERG comments

- Analysis of TONES 3 data for people who were/were not using primary OSA therapy at baseline shows solriamfetol cost-effective for both groups
- However, information on subgroups using/not using primary OSA therapy at baseline only available in [redacted] ([redacted]) of patients
- Small number of people ([redacted]) were not using primary OSA therapy at baseline
- Mean baseline ESS higher in those not using primary OSA therapy at baseline
- Analysis cannot distinguish according to reason for non-use of primary OSA therapy at baseline (e.g., CPAP intolerance, neurodegenerative or mental health conditions)

⊙ *Are analyses of solriamfetol alone compared with standard care appropriate for decision making in people who cannot tolerate CPAP?*

CPAP: continuous positive airway pressure; ESS: Epworth sleepiness scale; OSA: obstructive sleep apnoea

4. Adherence to primary OSA therapy [1]

- People may prefer drug treatment over primary OSA therapy. Use CPAP less → reduced benefit of solriamfetol plus CPAP
- Schweitzer 2020 showed no effect on adherence in TONES trials from baseline to week 4
- ERG noted analyses uncertain due to missing data and poor reporting → estimates not reported separately for those classified 'compliant' or 'non-compliant' at baseline

Committee: adherence to primary OSA therapy unlikely to be affected by solriamfetol. More data needed, with sensitivity analysis of impact of missing data across the 3 trials and subgroup analysis stratified by adherence at baseline

Company's consultation comments

- Compliance used as stratification factor in Schweitzer 2021 to minimise potential bias
- Data from Schweitzer 2021 considered missing is due to difference in way compliance was determined (electronically vs not). Missing data accounted for in standard way (LOCF)
- 'Worst case scenario': missing data for solriamfetol imputed as non-compliant; for placebo imputed as compliant. [redacted] hours by week 12 for people compliant at baseline having solriamfetol
- Compliance with primary OSA therapy met in 'worst case scenario' sensitivity analysis
- In line with draft NICE guideline for OSAHS, primary OSA therapy will be routinely monitored for people with OSA, therefore solriamfetol unlikely to increase resource use

CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea; OSAHS: obstructive sleep apnoea-hypopnoea syndrome; PAP: positive airway pressure; LOCF: last observation carried forward

4. Adherence to primary OSA therapy [2]

ERG comments

- **Uncertainty in company 'worst case scenario' analysis:**
  - Based on data from solriamfetol arm only (TONES 3)
  - Only for 'number of hours per night of use' and not other 2 measures of compliance
  - Reported up to 12 weeks of solriamfetol treatment. No analysis of long-term compliance
  - Missing data not "small": imputation increased patient numbers from [redacted] to [redacted]
- **Limitations with Schweitzer 2021[1] study:**
  - People included regardless of adherence to primary OSA therapy device. ERG would have preferred analysis stratified by adherence (to device use) at baseline
  - Unclear whether last observation-carried-forward approach was applied in the analysis in event of a missing data point for primary OSA therapy device usage
  - ~25% of patients had missing data for change from baseline analyses at last time period
- Company's ACD response only partly addresses uncertainties raised by ERG

⊙ *Is adherence to primary OSA therapy likely to be affected by solriamfetol?*

OSA: obstructive sleep apnoea

1. Journal of Clinical Sleep Medicine, Published Online version: February 1, 2021

5. Hospitalisation costs [1]

- Original company model did not include costs for serious adverse events
- ERG: some SAEs related to solriamfetol 150 mg led to hospitalisation. ERG included hospitalisation costs from TONES 5 in its base case

Committee: hospitalisation costs for serious adverse events should be included in model

Company's consultation comments

- Updated base-case applies hospitalisation rates from annualised data in TONES 3 for solriamfetol and SoC arms. Rates calculated from SAEs which led to hospitalisation irrespective of relationship to study drug → conservative approach
- TONES 3 more appropriate than TONES 5 because:
  - TONES 5 does not give difference between solriamfetol and placebo, only an absolute rate for solriamfetol, which may over-estimate hospitalisation costs
  - HES data annual hospitalisation rate for people having SoC is [redacted], and for stroke is [redacted]. These rates would be expected in a control arm of TONES 5, had one existed
  - TONES 5 hospitalisation rate included all events irrespective of a clear relationship to solriamfetol
- First PSUR for solriamfetol has been considered by EMA. The number of adverse drug reactions in people treated with solriamfetol in clinical practice is "relatively low"
- Provided scenario analyses with varying SAE-related hospital admission rates

EMA: European Medicines Agency; HES: Hospital Episode Statistics; PSUR: periodic safety update report; SAEs: serious adverse events; SoC: standard of care

5. Hospitalisation costs [2]

Hospitalisation rate assumptions in company scenario analyses

Company scenario	Solriamfetol			Source	SoC	Source
	37.5 mg	75 mg	150 mg			
Updated base case	[redacted]	[redacted]	[redacted]	TONES 3	[redacted]	TONES 3
Scenario 1	0%	0%	[redacted]	TONES 5 [a]	0%	N/A
Scenario 2	0%	0%	[redacted]	TONES 5 [a]	[redacted]	HES
Scenario 3	0%	0%	[redacted]	TONES 5 [b]	0%	N/A

[a] TONES 5 SAE-related hospitalisation irrespective of relationship to study drug
[b] Treatment-related SAEs leading to hospitalisation for solriamfetol from TONES 5

ERG comments

- Periodic Safety Update Report does not include event counts or give an overall figure for the frequency of SAEs or hospitalisations due to SAEs in the clinical trial programme
- Updated base case and scenario 2, with a higher rate of hospitalisation with standard care than with solriamfetol, are implausible
- Scenario 1 and scenario 3 are considered reasonable by ERG

NICE ⊙ *What hospitalisation rates are most appropriate to use in the model?*

HES: Hospital Episode Statistics; SAEs: serious adverse events; SoC: standard of care

6. Partner utility values [1]

- Company included partner utility values as scenario in its modelling, because of substantial impact that symptoms of OSA and its treatment can have on partners
- ERG: concerned about methods used to estimate partner utility values because time trade-off (TTO) utility estimates may not be comparable to those from the EQ-5D

Committee: partner utilities important to consider but not enough evidence to support inclusion. Would like sensitivity analysis to explore impact of partner utilities using EQ-5D

Company's consultation comments

- Conducted sensitivity analyses including partner utilities. Mapped from patient utility values to create partner utility values using TTO study algorithm
- Data including partner utilities presented to show ICER impact. As committee determined TTO study provided insufficient evidence to warrant inclusion, company has excluded partner utilities from updated base case → likely underestimates cost-effectiveness
- Insufficient time to carry out additional study using alternative methodology (e.g., EQ-5D)

ERG comments

- Health state descriptions in TTO place very high emphasis on daytime sleepiness
- Results unlikely comparable with EQ-5D utility values in other NICE appraisals
- Uncertainty over relationship between partner and patient utilities estimated from TTO

EDS: excessive daytime sleepiness; QALY; quality adjusted life year; OSA: obstructive sleep apnoea; TTO: time trade off

7. Dose split assumption

- Solriamfetol has 3 doses: 37.5 mg, 75 mg, 150 mg. Difficult to estimate likely split in practice
- Company base case: dose splits were 40%/40%/20% respectively for 37.5 mg/75 mg/150 mg solriamfetol doses. ERG base case used early US prescribing patterns = [redacted]

Committee: range of dose split assumptions included in the company's and ERG's analysis appropriate to account for variability in clinical practice

Company's consultation comments

- Updated base case uses ERG's preferred dose split
- However, company considers that greater proportion of people would likely have 37.5 mg dose in UK practice because:
  - In UK dose is unlikely to be increased after people normalise on a given dose. In TONES 3 around 52% of patients normalised on 37.5 mg dose
  - [redacted]
- Company provided other dose split scenarios (40/40/20, 33/33/33, and 20/40/40) alongside an investigation of the regression to the mean effect (issue 1)

ERG comments

- The company's revised base case is in line with ERG preference

⊙ *What is the most appropriate dose-split assumption?*

OSA: obstructive sleep apnoea

8. Prescribing setting

- Clinical experts suggested that solriamfetol would have to be started in specialist sleep clinics, but uncertain if longer-term prescribing could move to primary care
- Noted that if solriamfetol was recommended, the likely requirement for more monitoring of adherence to CPAP could put pressure on commissioned sleep services

Committee: solriamfetol likely to be limited to secondary care, but more information needed

Company's consultation comments

- Considers solriamfetol will be restricted to secondary care. Consistent with committee conclusion in ID1065: "pitolisant hydrochloride is likely to be prescribed in secondary care"
- Summary of product characteristics states treatment requires specialist initiation
- Common for people with OSA to remain in secondary/tertiary care, given nature of OSA
- Solriamfetol carries a black triangle (under additional monitoring), limiting its use in primary care. Also listed as a restricted 'Red' drug in formularies → prescription limited to hospitals
- NHS stakeholders outline preferred route for prescribing is outsourced outpatient pharmacy from secondary care
- BTS Clinical expert : "very unlikely that primary care would take on prescribing of this drug"

⊙ *Will solriamfetol be restricted to secondary care only prescribing?*

BTS: British Thoracic Society; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea

Equalities considerations

Equalities issues

- No equalities issues identified previously at scoping or technical engagement
- ACD consultation comment: Disability discrimination - there are many people who cannot work or live normal lives due to sleep apnoea and co-morbidities

⊙ *Are there any potential equalities issues?*

Summary of key assumptions in revised base cases

Assumption	Company	ERG-preferred assumptions
Placebo effect	Hawthorne effect (observation bias)	Observation bias, though company's RTM analysis subject to uncertainty
Utility values	ESS mapped to EQ-5D using NHWS	ESS mapped to EQ-5D using NHWS
Hospitalisation costs	Included: SAE rates from TONES 3 for solriamfetol and SoC arms	Included: Treatment-related rate ([redacted]) from TONES 5 for solriamfetol, zero rate for SoC
Partner utilities	Not included	Not included
Dose split assumption	[redacted]	[redacted]
Treatment response	≥2 point reduction in ESS	≥2 point reduction in ESS

ERG comments

- Revised base case reflects committee's preferred assumptions listed in ACD section 3.16
- Although, SAE hospitalisation costs included in the company revised base case differ from the ERG's preferred estimates

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ESS: Epworth sleepiness scale; NHWS: National Health and Wellness Survey; RTM: regression to the mean; SAE: serious adverse event; SoC: standard of care

Company base case results (with solriamfetol PAS)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Deterministic					
SoC	£4,810	11.524			
SoC + solriamfetol	[redacted]	11.969	[redacted]	0.445	[redacted]
Probabilistic					
SoC	£4,873	11.866			
SoC + solriamfetol	[redacted]	12.398	[redacted]	0.531	[redacted]

ERG comments

- Deterministic sensitivity analysis indicates that results are most sensitive to uncertainty over the following parameters (with ICERs above the £20,000 per QALY threshold at either the upper or lower parameter limit):
  - [redacted]
  - [redacted]
  - [redacted]

ESS: Epworth sleepiness scale; NHWS: National Health and Wellness Survey; PAS: patient access scheme; SAE: serious adverse event; SoC: standard of care

Company's deterministic scenario analyses (with solriamfetol PAS) [1]

Scenario	Issue	Incremental		ICER (£/QALY)
		Costs (£)	QALYs	
Company base case	N/A	[redacted]	0.445	[redacted]
1. 100% true placebo	Placebo effect	[redacted]	0.699	[redacted]
2. 33% regression to the mean/67% Hawthorne	Placebo effect	[redacted]	0.394	[redacted]
3. 33% regression to the mean/60% true placebo/7% Hawthorne	Placebo effect	[redacted]	0.546	[redacted]
4. McDaid ESS to EQ-5D mapping	Utilities	[redacted]	0.383	[redacted]
5. Time trade off	Utilities	[redacted]	0.952	[redacted]
6. Using primary OSA therapy at baseline	Population	[redacted]	0.415	[redacted]
7. Not using primary OSA therapy at baseline	Population	[redacted]	0.521	[redacted]
8. Compliant with primary OSA therapy at baseline	Population	[redacted]	0.393	[redacted]
9. Not compliant with primary OSA therapy at baseline	Population	[redacted]	0.550	[redacted]

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ESS: Epworth sleepiness scale; OSA: obstructive sleep apnoea: PAS; patient access scheme

Company's deterministic scenario analyses (with solriamfetol PAS) [2]

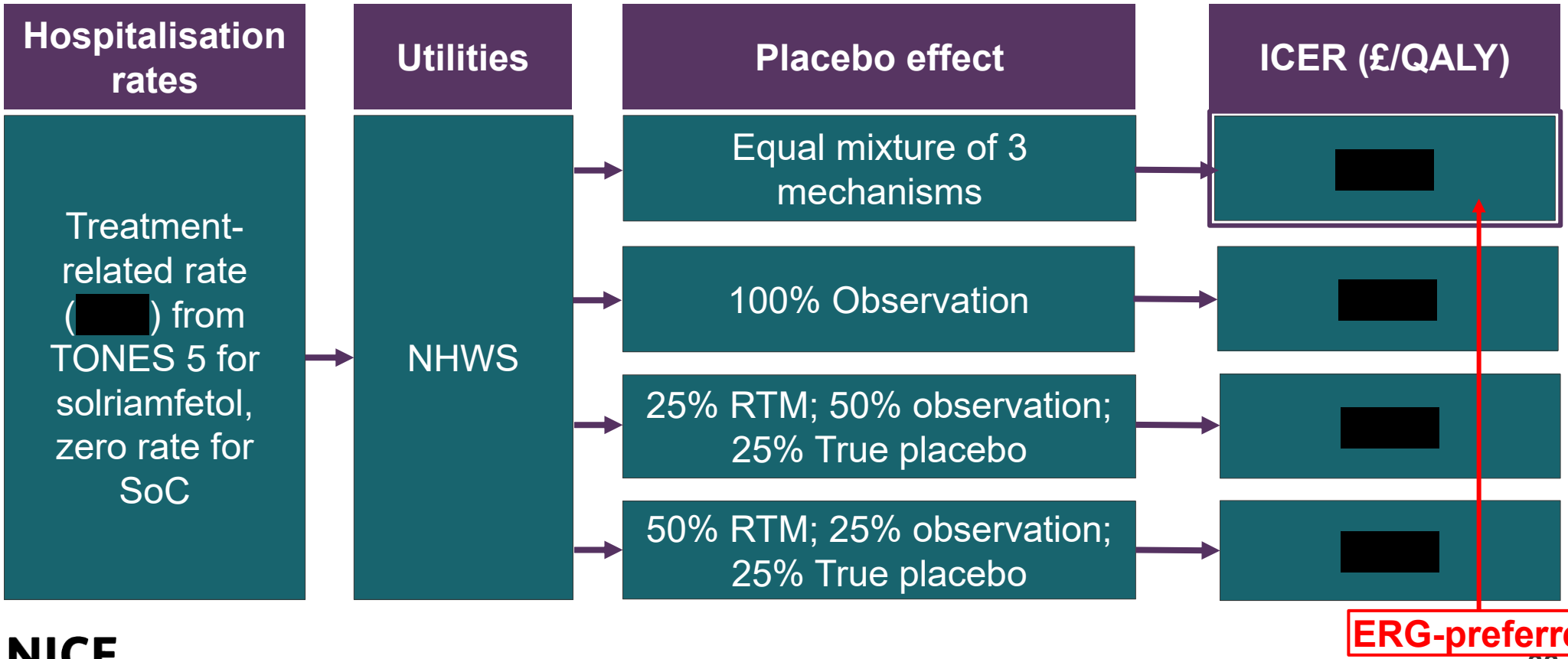
Scenario	Issue	Incremental		ICER (£/QALY)
		Costs (£)	QALYs	
Company base case	N/A	[redacted]	0.445	[redacted]
10. Any SAE rate for solriamfetol arm, zero rate for SoC	Hospitalisation costs	[redacted]	0.445	[redacted]
11. Any SAE rate for solriamfetol arm, HES rate for SoC	Hospitalisation costs	[redacted]	0.445	[redacted]
12. Treatment-related rates for solriamfetol arm, zero rate for SoC	Hospitalisation costs	[redacted]	0.445	[redacted]
13. NHWS ESS to EQ-5D mapping	Partner utility values	[redacted]	0.609	[redacted]
14. McDaid ESS to EQ-5D mapping	Partner utility values	[redacted]	0.524	[redacted]
15. Time trade off	Partner utility values	[redacted]	1.303	[redacted]
16. 40/40/20	Dose split assumption	[redacted]	0.411	[redacted]
17. 33/33/33	Dose split assumption	[redacted]	0.464	[redacted]
18. 20/40/40	Dose split assumption	[redacted]	0.501	[redacted]

NICE

ESS: Epworth sleepiness scale; HES: Hospital Episode Statistics; NHWS: National Health and Wellness Survey; PAS: patient access scheme; SAE: serious adverse event; SoC: standard of care

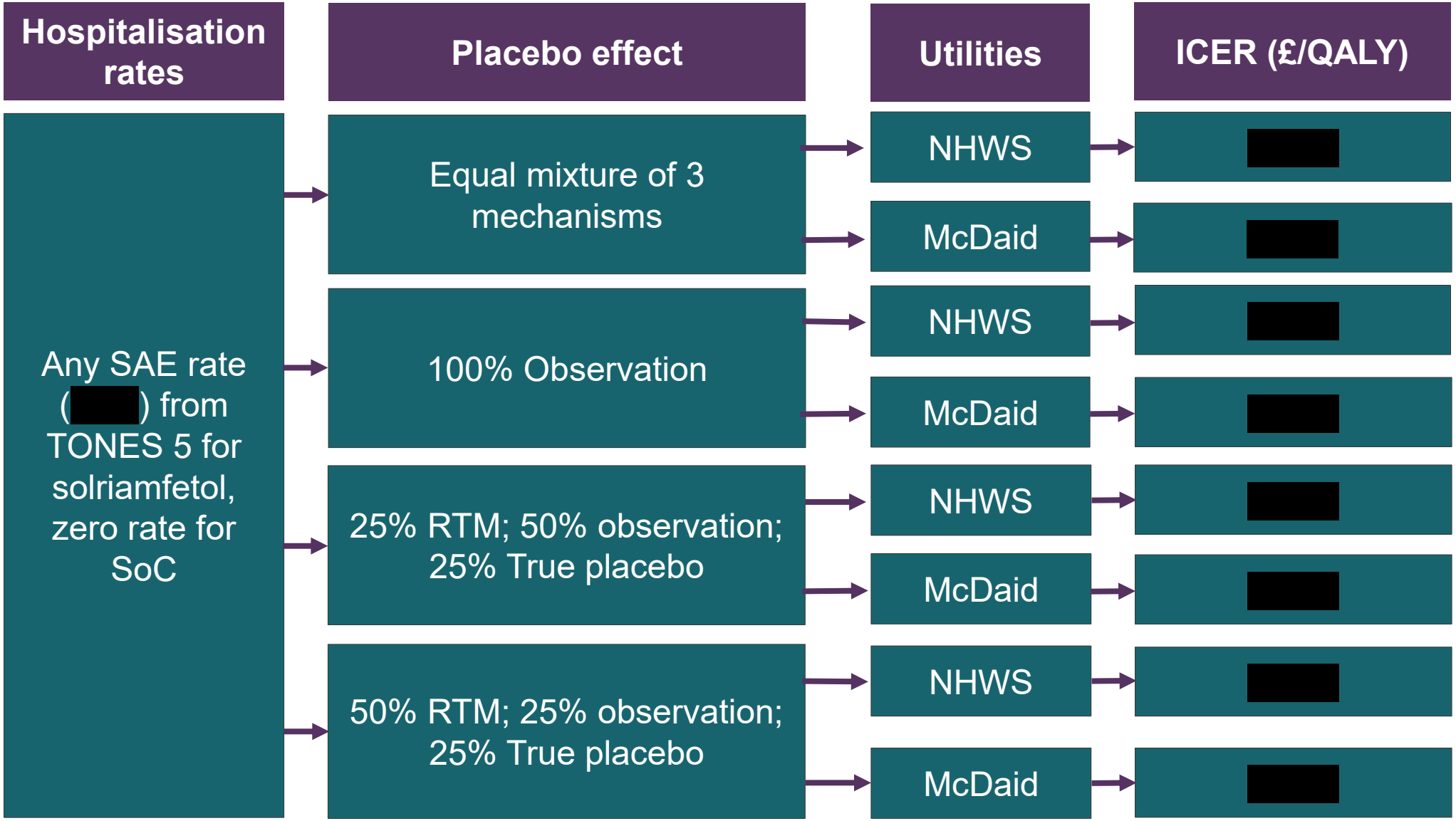
ERG deterministic scenario analyses (with PAS) [1]

Scenario	Issue	Incremental		ICER (£/QALY)
		Costs (£)	QALYs	
Company base case	N/A	[redacted]	0.445	[redacted]
19. 100% regression to the mean	Placebo effect	[redacted]	0.290	[redacted]
20. Equal mixture of the 3 placebo mechanisms	Placebo effect	[redacted]	0.478	[redacted]



NHWS: National Health and Wellness Survey; PAS: patient access scheme; RTM: regression to the mean; SoC: standard of care

ERG deterministic scenario analyses (with PAS) [2]



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NHWS: National Health and Wellness Survey; PAS: patient access scheme; RTM: regression to the mean; SoC: standard of care

Back-up

Clinical trial results – TONES 3

Mean change in ESS from baseline weeks 1,4,8,12

Placebo

Soliramfetol 37.5mg

Soliramfetol 75mg

Soliramfetol 150mg

Mean change in MWT from baseline weeks 1,4,12

Soliramfetol 150mg

Soliramfetol 75mg

Soliramfetol 37.5mg

Placebo

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*p<0.05, †p<0.0001 vs. placebo ESS: MWT:

TONES 3 trial design

TONES 3 (NCT02348606) is the pivotal phase III RCT in patients with EDS due to OSA

Patients enrolled n=476

- 18-75 years of age.
- BMI 18-45.
- Diagnosis of OSA according to ICSD3-criteria*.
- Baseline ESS score ≥10

Key exclusions

- Pregnant women.
- Presence/history of significant unstable medical conditions (Psychiatric, surgical).
- Presence/history of cardiovascular disease.

TONES 3

Phase III RCT, double blinded

Solriamfetol (37.5mg, 75mg, 150mg and 300mg)**

Placebo (oral tablet)

Endpoints

Used in economic model

Primary

- Change in Epworth Sleepiness Scale (ESS)***.
- Change in Maintenance of Wakefulness Test (MWT).

Secondary

- Patient Global Impression of Change (PGIc).
- Change in sleep latency time.

HRQoL measures used

- FOSQ10
- SF-36v2
- EQ-5D-5L

*ICSD-3 is the International Classification of Sleep Disorders

**300mg solriamfetol dose is unlicensed

*** A self administered questionnaire used by doctors to assess daytime sleepiness. The person completing the questionnaire rates how likely they are to doze off during the day in different situations. Chance of falling asleep rated on a 0-3 scale (3 being high chance)

Company trial results – TONES 3

TONES 3 – Phase III RCT *Solriamfetol compared to placebo (12 week data)-300mg excluded*				
12-week results	**Placebo N=114**	**Solriamfetol 37.5 mg N=56**	**Solriamfetol 75 mg N=58**	**Solriamfetol 150 mg N=116**
Change in ESS score from baseline (SE)	−3.3 ([redacted])	−5.1 ([redacted])	−5.0 ([redacted])	−7.7 ([redacted])
P value	N/A	0.0161	0.0233	<0.0001
Proportion of patients with a reduction from baseline ESS of ≥3 at week 12	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	4 (3.4%)	3 (5.2%)	2 (3.2%)	5 (4.3%)

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AEs: adverse events; ESS: Epworth Sleepiness Scale; SE: standard error

Clinical trial results – TONES 3 – QoL measures

[redacted]

	Solriamfetol		
	37.5 mg N=56	75 mg N=58	150 mg N=116
Change in FOSQ-10 total score from baseline to week 12			
LS mean difference vs placebo	[redacted]	[redacted]	1.22
p value	[redacted]	[redacted]	[redacted]
Change in SF-36v2 physical component summary score from baseline to week 12			
LS mean difference vs. placebo	[redacted]	[redacted]	2.07
p value (nominal)	[redacted]	[redacted]	[redacted]
Change in SF-36v2 mental component summary score from baseline to week 12			
LS mean difference vs. placebo	[redacted]	[redacted]	2.05
p value (nominal)	[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L Index from baseline to week 12			
LS mean difference vs. placebo	[redacted]	[redacted]	[redacted]
p value (nominal)	[redacted]	[redacted]	[redacted]

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LS: least squares

Additional trials - TONES 4 & 5

Tones 4: Phase 3 study with a double blind, placebo controlled, randomised withdrawal phase to evaluate the effect of abrupt solriamfetol withdrawal.

Tones 5:

- Long-term (1-year) open label, Phase 3 extension study. This study contained a 2 week, double blind, placebo controlled randomised withdrawal component.
- Patients in TONES 5 had either OSA or narcolepsy (Safety Population: n=417 OSA; n=226 narcolepsy).

TONES 5 change in mean ESS scores from baseline for patients with OSA for the solriamfetol 75 mg and 150 mg dose (Safety population)

Change from baseline (SD)[a]	Group A (from TONES 3)		Group B (from TONES 4)	
	75 mg	150 mg	75 mg	150 mg
At week 2	[redacted]	[redacted]	[redacted]	[redacted]
At week 40	[redacted]	[redacted]	NA	NA
At week 52	NA	NA	[redacted]	[redacted]

- Group A (n=519; 81%) included patients from TONES 2 and TONES 3.
- Group B (n=124; 19%) included patients from TONES 4, or one of the phase 2 studies or TONES 1.

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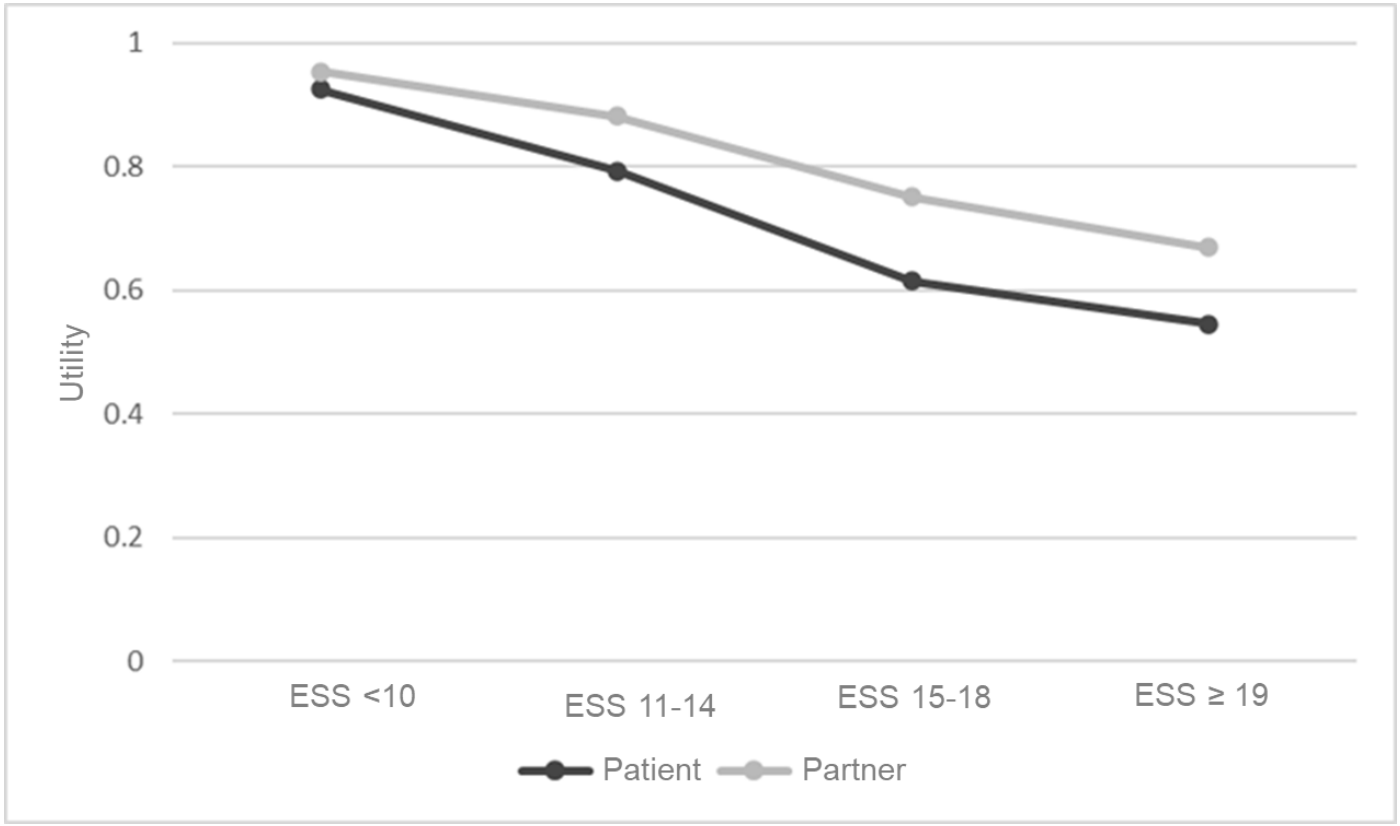
ESS: Epworth Sleepiness Scale; OSA: obstructive sleep apnoea; SD: standard deviation

Relationship between EQ 5D and ESS score based on McDaid and NHWS algorithms

ESS: Epworth Sleepiness Scale; NHWS: National Health and Wellness Survey

Mean TTO utility values for patients and partners by health state



Mean utility values NHWS, McDaid and TTO, for patients by health state using the NHWS ESS categorisation

ESS: Epworth Sleepiness Scale; NHWS: National Health and Wellness Survey: TTO: time trade off

Utility values from ID1605 Pitolisant hydrochloride for treating excessive daytime sleepiness caused by OSA

State	Utility value: mean
Health states with pitolisant - HAROSA I (EQ-5D-3L)	
OSAHS	0.803
Post-CHD	0.75
Post-stroke	0.739
Health states with pitolisant - HAROSA II (EQ-5D-3L)	
OSAHS	0.802
Post-CHD	0.750
Post-stroke	0.739
Health states with BSC – HAROSA I (EQ-5D-3L)	
OSAHS	0.777
Post-CHD	0.725
Post-stroke	0.714
Health states with BSC – HAROSA II (EQ-5D-3L)	
OSAHS	0.775
Post-CHD	0.723
Post-stroke	0.712
Scenario analysis: Health states with MAD – HAROSA II (EQ-5D-3L)	
OSAHS	0.789
Post-CHD	0.737
Post-stroke	0.726

Sensitivity analysis considering alternative placebo mechanisms [redacted] dose split)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	90%	[redacted]	[redacted]	[redacted]				
	100%	[redacted]						

Hospitalisation rates backing data

Company scenario	Solriamfetol			Source	SoC	Source
	37.5 mg	75 mg	150 mg			
Updated base case	[redacted]	[redacted]	[redacted]	TONES 3	[redacted]	TONES 3
Scenario 1	0%	0%	[redacted]	TONES 5 [a]	0%	N/A
Scenario 2	0%	0%	[redacted]	TONES 5 [a]	[redacted]	HES
Scenario 3	0%	0%	[redacted]	TONES 5 [b]	0%	N/A

- [redacted] in the company updated base case for solriamfetol 37.5mg is based on [redacted] of solriamfetol-treated patients hospitalised for SAE up to week 12 in TONES 3
- [redacted] in the company updated base case for solriamfetol 75mg is based on [redacted] of solriamfetol treated patients hospitalised for SAE up to week 12 in TONES 3
- [redacted] in the company updated base case for solriamfetol 150mg is based on [redacted] of solriamfetol treated patients hospitalised for SAE up to week 12 in TONES 3
- [redacted] in the company updated base case for placebo is based on [redacted] of placebo treated patients hospitalised for SAE up to week 12 in TONES 3
- [redacted] in scenarios 1 and 2 is based on ([redacted]) of solriamfetol-treated patients hospitalised for SAEs in TONES 5
- [redacted] in scenario 3 for solriamfetol 150mg is based on [redacted] of solriamfetol treated patients hospitalised for a treatment-related SAE in TONES 5