NICE National Institute for Health and Care Excellence

For public – Fully redacted

CORRECTED – 14 December 2021

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

Chair's presentation

3rd Appraisal committee meeting

14 December 2021

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 • List price minimum cost per year £1,154: max £3,241 • [redacted]

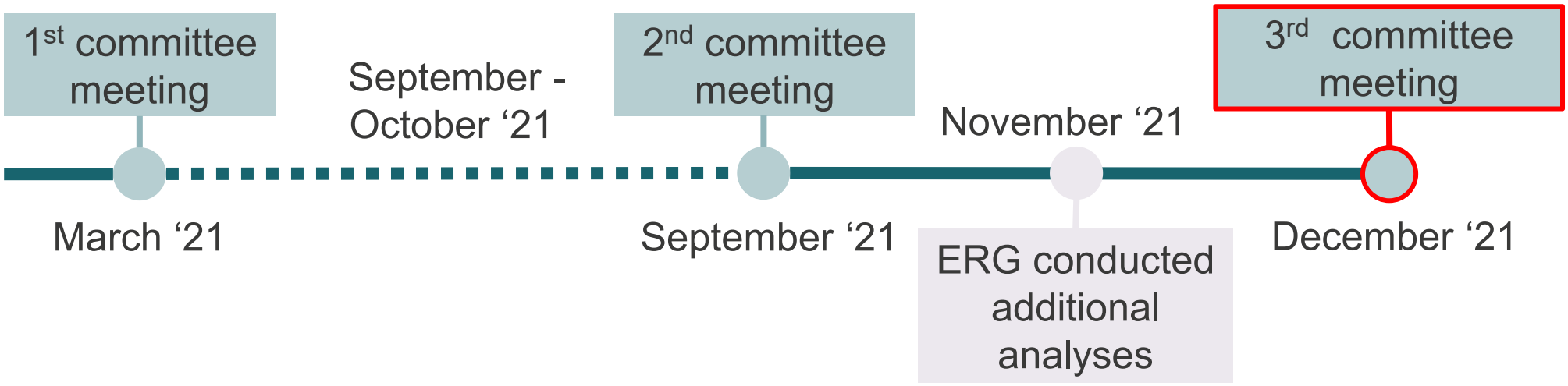
*Jazz Pharmaceuticals has agreed a PAS discount with NHS England for solriamfetol

PAS: patient access scheme

ACD current recommendation

Solriamfetol 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)

History



Placebo effect
- 100% Hawthorne
- Regression to the mean
- True placebo effect
- 33% mix of each

Utility values
- ESS mapped using McDaid
- Trial EQ-5D
- 50% mix of each using average of utility values or average of coefficients

ESS, Epworth Sleepiness Scale

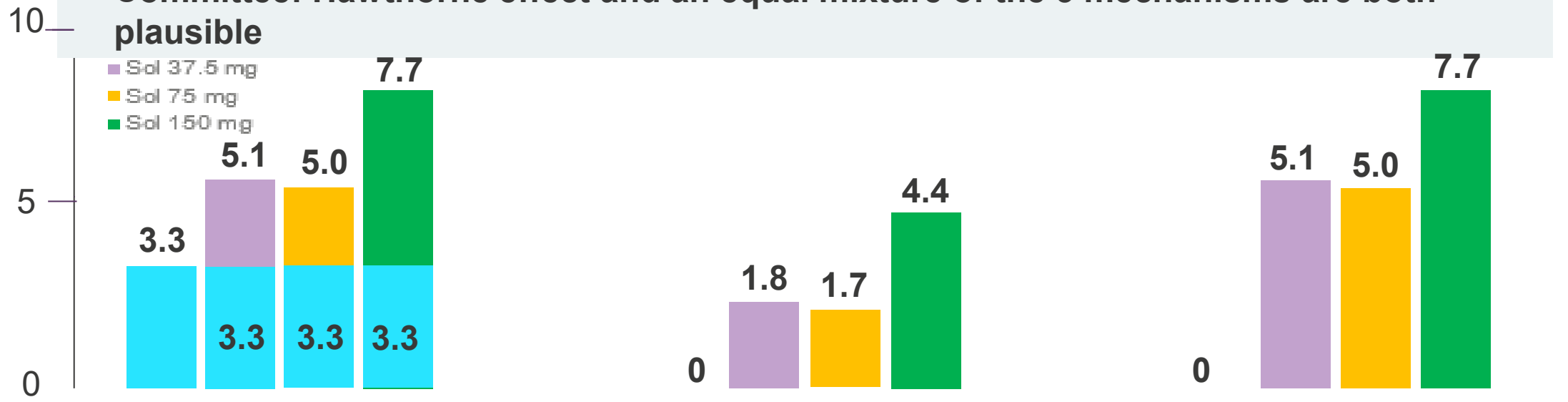
Summary

Issue		Description
1	Placebo effect	• Hawthorne effect (committee preference at ACM2) • Regression to the mean • True placebo effect • 33% mix of each (committee preference at ACM2) ? Which adjustment for the placebo effect is most appropriate?
2	Utility values	• ESS mapped to EQ-5D using McDaid • ESS mapped to EQ-5D using NHWS • EQ-5D values from trial • Average of ESS mapped and trial EQ-5D [ACM2 pref] ➢ Average of utility values [method 1] ➢ Average of coefficients [method 2] ? Should utility values be based on trial EQ-5D, ESS mapped using McDaid, or an average of the 2?

Issue 1: Placebo effect (1/2)

Issue background

- In TONES 3 a reduction in Epworth sleepiness scale (ESS) score of 3.3 observed in control 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 control arm
- **Committee: Hawthorne effect and an equal mixture of the 3 mechanisms are both plausible**



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

Issue 1: Placebo effect (2/2)

- Hawthorne effect
- Regression to the mean
- True placebo effect
- 33% mix of each

Which adjustment for the placebo effect is most appropriate?

Issue 2: Utility values (1/8)

Issue background

- Company collected EQ-5D in TONES 3 → [redacted] between treatment arms
- ACM1: Committee requested analysis using SF-36 data collected in TONES 3
- ACM2: Company did not provide SF-36 data. Maintained its base case which used NHWS mapping to estimate EQ-5D from ESS
- The committee concluded, given the uncertainty, the quality of life benefit should be the average of the EQ-5D utilities from TONES 3 and the utilities mapped using McDaid

ESS: Epworth sleepiness scale; NHWS: National Health and Wellness Survey

Issue 2: Utility values (2/8)

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]	[redacted]
	Non-responder year 1		[redacted]	[redacted]	[redacted]
	Non-responder year 2+			[redacted]	
McDaid algorithm	Responder	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder year 1		[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

Issue 2: Utility values (3/8)

Issue background

Following NICE technical team request, company provided EQ-5D from TONES 3 for solriamfetol and placebo arms and overall population using pooled data

Utility values for responders and non-responders to placebo, solriamfetol, and overall population in TONES 3 (ESS >12) using trial data – TONES 3 population [see backup for subgroups]

Arm	Response Strata	Mean EQ-5D at baseline	Mean EQ-5D at week 12	Mean EQ-5D change
Solriamfetol	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Placebo	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Pooled placebo and solriamfetol	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]

Company concerns

- Placebo treated patients from trial would not be considered responders in practice → in practice they are not prescribed anything → they receive existing standard of care
- Stratification of placebo into responders and non-responder inappropriate → pooling in this way **does not** represent clinical practice

Issue 2: Utility values (4/8)

ERG analysis

ERG explored 2 methods for averaging the TONES 3 and McDaid mapping utilities:
Method 1: baseline utility for both treatment arms [redacted], adjusted for responders and non-responders. Gives utility estimates of [redacted] for responders and [redacted] for non-responders, irrespective of treatment arm
Method 2: McDaid ESS to EQ-5D with slope coefficient replaced with the ERG's estimate of the mean change in EQ-5D utility per unit change in ESS. Coefficient from the analysis by McDaid and colleagues was -0.0096984 and the ERG estimate from TONES 3 [redacted]. Utility estimates differ by treatment arm and dose. *Using subgroups: Addon to CPAP is* [redacted], *CPAP non-users* [redacted]

- Method 2 gives bigger differences than method 1, because the former takes account of between-arm differences in mean ESS within the responder and non-responder groups
- In the Hawthorne model, the mean change in ESS observed in the standard care arm is subtracted from final ESS results from all arms (centred data) → mean changes in ESS used in this version of the model are lower than those reported by the ERG

Company

- Company unfamiliar with approach, and whether it reflects DSU guidance
- Weighting by 50/50 not explained robustly
- Approach lacks transparency & unconventional → creates ambiguity in interpretation of independent utility sources → uncertainty should be conventionally assessed using separate scenarios

NICE ESS: Epworth sleepiness scale

Issue 2: Utility values (5/8)

Company

- Using trial EQ-5D inappropriate → Prefer approach using NHWS analysis
- TONES 3 mean baseline utility was [redacted] and [redacted] for responders and non-responders, indicating that there was limited room for patients to achieve a utility gain in response to treatment
- Given burden of EDS, baseline values are inconsistent with utility profile that would be expected in this patient population
- [redacted]% of patients had baseline utility of 1, which increased at week 12 to [redacted]% → indicates reducing the **ceiling effect** may have allowed a greater improvement in EQ-5D than was possible in the trial
- The ceiling effect means that due to high baseline utility scores, there is minimal room for utility scores to improve during the trial. Utilities for both mapping approaches:

		Mean baseline EQ-5D	Mean Wk 12 EQ-5D	Difference
NHWS	Responders	[redacted]	[redacted]	[redacted]
	Non-responders	[redacted]	[redacted]	[redacted]
McDaid	Responders	[redacted]	[redacted]	[redacted]
	Non-responders	[redacted]	[redacted]	[redacted]

Issue 2: Utility values (6/8)

Company on ceiling effects

- Undertook analysis to estimate potential utility improvement by accounting for **ceiling effect** for TONES 3 →
- Random samples from TONES 3 data to generate mean baseline and week 12 EQ-5D Simulations with baseline utility of +/- 0.005 points from previous CPAP studies were averaged → demonstrated what might happen to week 12 utilities in TONES 3 had baseline utilities been like those in previous studies
- If responders in TONES 3 had baseline utility of 0.74 (from Mar 2003) instead of 0.838 from TONES 3, their EQ-5D improvement would have been approximately [redacted] instead of [redacted] → Not dissimilar to scores predicted for responders using NHWS

Utility values predicted using an assumed baseline utility from an alternative OSA study*

Study baseline simulated in TONES 3		Baseline EQ-5D in reference study	Mean ESS improvement in TONES 3	Simulated Baseline EQ-5D	Wk 12 EQ-5D in TONES 3	Difference
Mar 2003	CPAP: responders	0.74	[redacted]	[redacted]	[redacted]	[redacted]
	CPAP: non-responders	0.74	[redacted]	[redacted]	[redacted]	[redacted]

*company also provided analysis with 3 other study baseline values; Jenkinson 1997/1998, Chakravorty 2002, and McMillan 2014

Issue 2: Utility values (7/8)

ERG on ceiling effects

- ERG believes 'ceiling effect' analysis are highly uncertain and likely to be biased
- Population EQ-5D is 0.9345 (95% CI: 0.927 to 0.941) with no history of health condition and 0.8344 (0.824 to 0.843) with a history of health condition
- Alternative OSA studies (Jenkinson 1997/1998, Chakravorty 2002, Mar 2003 and McMillan 2014) also used EQ-5D, and susceptible to a ceiling effect as the TONES 3 → Not clear why EQ-5D values from selected reference trials would be more accurate
- Company analysis is a form of calibration → can be as an appropriate modelling technique
- Company used baseline before CPAP use, doesn't align with current population who were on primary OSA therapy

Company response on ceiling effects

- Fang et al (2021) → suggests EQ-5D-5L may have large ceiling & 'does not include positive aspects of health such as energy or well-being' → energy important in context of EDS/OSA
- Baseline utilities from selected studies more appropriate before CPAP than post treatment because population include people who '*have not been satisfactorily managed*'. Post-treatment will estimate utility in patients with residual EDS
- Also ceiling effects in these studies less likely because values are lower

Issue 2: Utility values (8/8)

Company – general comments

- Unclear why no weight given to NHWS → ERG originally preferred this
- Noted committee's concern that NHWS based on cross-sectional data, and not an analysis of change scores → but NICE DSU do not say that cross-sectional mapping is inappropriate
    - Agree non-randomised data has issues of omitted variables → but do not agree it should be discarded. DSU guidelines suggest relevant studies can include observational studies
- 2 appraisals (TA665 [upadacitinib for RA] and TA565 [benralizumab for arthma]) used mapping based on longitudinal data which did not use change scores
- Noted committee's concern NHWS utility were not plausible because utilities were high when ESS was extremely high:
    - Cttee view inconsistent with ERG view that QOL underestimated
    - Using NHWS algorithm, mapping ESS scores of 0-24 to QOL gives utility values of [redacted] to [redacted] → not implausible → trial EQ-5D substantially higher
- ERG stated that time trade off (TTO) did not allow for appropriate comparisons across technologies because of emphasis on sleep in study. Study was conducted to supplement evidence → although not the most appropriate source, shows impact on ICERs & that EQ-5D underestimated QOL
- EQ-5D showed lack of responsiveness to change in primary endpoint → has provided substantial evidence that its insufficient to measure QOL improvement

Should utility values be based on trial EQ-5D, ESS mapped using McDaid or NHWS, or an average?

Deterministic cost-effectiveness results

ITT population

Scenario	Incremental		ICER (£/QALY)
	Costs (£)	QALYs	
Company base case (NHWS + 100% Hawthorne)	[redacted]	0.445	[redacted]
+ treatment-related hospitalisation rates from TONES 5 for solriamfetol, no cost for standard care	[redacted]	0.445	[redacted]
100% Hawthorne			
1. Utility values from trial EQ-5D	[redacted]	0.014	[redacted]
2. Utility values from ESS mapped to EQ-5D using McDaid	[redacted]	0.383	[redacted]
3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1)	[redacted]	0.266	[redacted]
4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2)	[redacted]	0.251	[redacted]
Equal mix of 3 placebo models			
1. Utility values from trial EQ-5D	[redacted]	0.066	[redacted]
2. Utility values from ESS mapped to EQ-5D using McDaid	[redacted]	0.463	[redacted]
3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1)	[redacted]	0.277	[redacted]
4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2)	[redacted]	0.303	[redacted]

CORRECTED

Deterministic cost-effectiveness results

Add on to CPAP (from TONES 3 subgroup [redacted])

Scenario	Incremental		ICER (£/QALY)
	Costs (£)	QALYs	
Company base case (NHWS + 100% Hawthorne)	[redacted]	[redacted]	[redacted]
+ treatment-related hospitalisation rates from TONES 5 for solriamfetol, no cost for standard care	[redacted]	[redacted]	[redacted]
100% Hawthorne			
1. Utility values from trial EQ-5D	[redacted]	[redacted]	[redacted]
2. Utility values from ESS mapped to EQ-5D using McDaid	[redacted]	[redacted]	[redacted]
3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1)	[redacted]	[redacted]	[redacted]
4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2)	[redacted]	[redacted]	[redacted]
Equal mix of 3 placebo models			
1. Utility values from trial EQ-5D	[redacted]	[redacted]	[redacted]
2. Utility values from ESS mapped to EQ-5D using McDaid	[redacted]	[redacted]	[redacted]
3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1)	[redacted]	[redacted]	[redacted]
4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2)	[redacted]	[redacted]	[redacted]

CORRECTED

Deterministic cost-effectiveness results

CPAP non-users (from TONES 3 subgroup [redacted])

Scenario	Incremental		ICER (£/QALY)
	Costs (£)	QALYs	
Company base case (NHWS + 100% Hawthorne)	[redacted]	[redacted]	[redacted]
+ treatment-related hospitalisation rates from TONES 5 for solriamfetol, no cost for standard care	[redacted]	[redacted]	[redacted]
100% Hawthorne			
1. Utility values from trial EQ-5D	[redacted]	[redacted]	[redacted]
2. Utility values from ESS mapped to EQ-5D using McDaid	[redacted]	[redacted]	[redacted]
3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1)	[redacted]	[redacted]	[redacted]
4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2)	[redacted]	[redacted]	[redacted]
Equal mix of 3 placebo models			
1. Utility values from trial EQ-5D	[redacted]	[redacted]	[redacted]
2. Utility values from ESS mapped to EQ-5D using McDaid	[redacted]	[redacted]	[redacted]
3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1)	[redacted]	[redacted]	[redacted]
4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2)	[redacted]	[redacted]	[redacted]

Back up slides

Issue 1: Placebo effect (Background)

First committee meeting

- Committee acknowledged there may be some RTM
- Wanted to see threshold analysis assuming RTM effect

Company's consultation comments

- Provided scenario analysis exploring RTM over range of contribution (0% to 33%)
- Provided evidence against RTM:
  - TONES 3 onset of placebo effect (1 week) too rapid for RTM
  - 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

Second committee meeting

- Committee concluded it was reasonable to consider both the company base case (100% Hawthorne) and an ERG scenario in which the improvement in TONES 3 control arm was attributed equally between the 3 potential mechanisms (Hawthorne, RTM and true placebo)

Which method to adjust for improvement in the control arm of TONES 3 is most appropriate?

RTM: regression to the mean

Issues 2. Utilities (background)

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

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

Utility values predicted using an assumed baseline from alternative OSA studies

Study baseline simulated in TONES 3		Baseline EQ-5D in reference study	Mean ESS improvement in TONES 3	Simulated Baseline EQ-5D†	Wk 12 EQ-5D in TONES 3	Difference
Jenkinson 1997/1998	CPAP: responders	0.79	[redacted]	[redacted]	[redacted]	[redacted]
	CPAP: non-responders	0.79	[redacted]	[redacted]	[redacted]	[redacted]

NICE

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

Utility values predicted using an assumed baseline from alternative OSA studies

Study baseline simulated in TONES 3		Baseline EQ-5D in reference study	Mean ESS improvement in TONES 3	Simulated Baseline EQ-5D†	Wk 12 EQ-5D in TONES 3	Difference
Chakravorty 2002	CPAP: responders	0.73	[redacted]	[redacted]	[redacted]	[redacted]
	CPAP: non-responders	0.73	[redacted]	[redacted]	[redacted]	[redacted]
	Lifestyle advice: responders	0.77	[redacted]	[redacted]	[redacted]	[redacted]
	Lifestyle advice: non-responders	0.77	[redacted]	[redacted]	[redacted]	[redacted]

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

Utility values predicted using an assumed baseline from alternative OSA studies

Study baseline simulated in TONES 3		Baseline EQ-5D in reference study	Mean ESS improvement in TONES 3	Simulated Baseline EQ-5D†	Wk 12 EQ-5D in TONES 3	Difference
McMillan 2014	CPAP: responders	0.666	[redacted]	[redacted]	[redacted]	[redacted]
	CPAP: non-responders	0.666	[redacted]	[redacted]	[redacted]	[redacted]
	BSC: responders	0.668	[redacted]	[redacted]	[redacted]	[redacted]
	BSC: non-responders	0.668	[redacted]	[redacted]	[redacted]	[redacted]

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

Arm	Response Strata	Mean EQ-5D at baseline	Mean EQ-5D at week 12	Mean EQ-5D change
Solriamfetol (n=166)	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Placebo (n=94)	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Pooled (n=260)	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]

Arm Add on to CPAP	Response Strata	Mean EQ-5D at baseline	Mean EQ-5D at week 12	Mean EQ-5D change
Solriamfetol (n=[redacted])	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Placebo (n=[redacted])	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Pooled (n=[redacted])	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]

Arm CPAP non-users	Response Strata	Mean EQ-5D at baseline	Mean EQ-5D at week 12	Mean EQ-5D change
Solriamfetol (n=[redacted])	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Placebo (n=[redacted])	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Pooled (n=[redacted])	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]