NICE National Institute for Health and Care Excellence

Public observer slides – no confidential information

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

Lead team presentation

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Company: Jazz Pharmaceuticals

[10/03/2021]

Excessive waketime sleepiness (Obstructive sleep apnoea)

Overview of the condition

- Excessive waketime sleepiness (also known as hypersomnia) means people struggle to stay awake and alert during the day (or equivalent waking hours)
  - leads to an irrepressible need to sleep or unintended lapses into drowsiness or sleep.
- One cause of excessive daytime sleepiness (EDS) is obstructive sleep apnoea (OSA),
  - OSA is a chronic, common sleep disorder, characterised by the repeated occurrence of complete (apnoea) or partial (hypopnoea) closures of the upper airway during sleep.
  - An estimated 1.5 million adults in the UK have OSA, equating to 2.32% of the overall population; of these approximately 22% are diagnosed and treated.
  - can affect many aspects of daily life, including education, employment, driving, relationships and emotional health and general health.
  - OSA negatively impacts sleep quality and may result in napping, decreased energy, irritability, feeling unrefreshed or having headaches upon awakening, reduced enjoyment of usual activities, and impaired work performance.

Solriamfetol (Sunosi, Jazz Pharmaceuticals)

Mechanism of action	Solriamfetol is a derivative of the amino acid phenylalanine. The mechanism by which solriamfetol exerts its wake-promoting effects in humans is yet to be fully characterised but is thought to be through activity as a 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 (CPAP)
Dosage and Administration	Tablet, 37.5mg, 75mg or 150mg once daily
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

Issues after technical engagement

Key Issues identified prior to technical engagement	Description of the issue	Impact	Status
Issue 1: Potential reduction in compliance with primary OSA therapy during solriamfetol treatment	Determining effect of Solriamfetol on compliance to primary OSA therapy		**Unresolved**
Issue 2: Model population; ESS level	What is the ESS level for “Normal” while on treatment		**Resolved**
Issue 3: Definition of treatment response	What magnitude of ESS improvement is appropriate for a treatment response		**Partially resolved**
Issue 4: Adjustment of ESS for the placebo effect (‘centring’)	How should the placebo effect adjustment be dealt with		**Unresolved**
Issue 5: Health utility values	Appropriate source of derivation for EQ-5D values		**Partially resolved**
Issue 6: Partner utilities	Should these be considered in the analysis		**Partially resolved**
Issue 7: Treatment discontinuation and loss of response rates	Should this be dose dependent or constant across doses		**Unresolved**
Issue 8: Adverse event costs	Should costs leading to hospitalisation be included		**Partially resolved**
Issue 9: Solriamfetol dose split	What is the correct does split for the UK		**Partially resolved**

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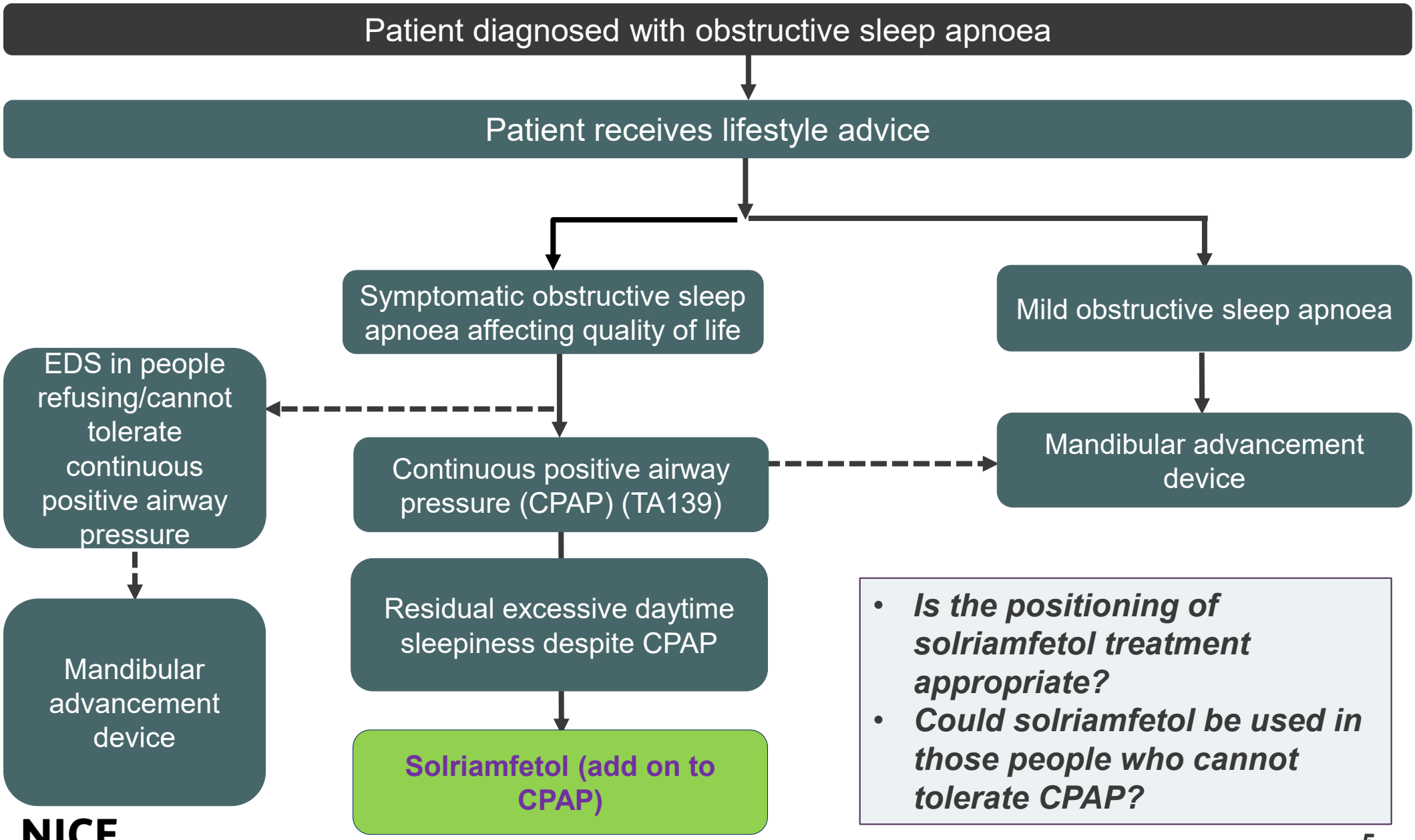
Key:
Model driver;  Unknown impact;  Small/moderate impact 

Treatment Pathway – Current and proposed with solriamfetol



- ***Is the positioning of solriamfetol treatment appropriate?***
- ***Could solriamfetol be used in those people who cannot tolerate CPAP?***

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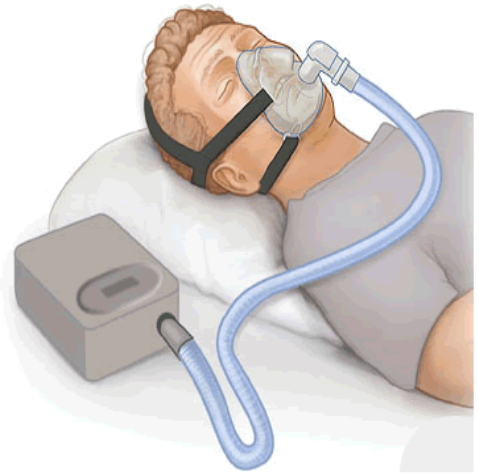
Patient and carer perspectives

The Sleep Apnoea Trust Association (SATA)



Overview

- Can be very debilitating and take a toll on patients and family members.
- Poor understanding of the condition amongst some primary care professionals.
- Diagnosis and referral can be delayed, sleep clinic referral is not necessarily the first consideration for a GP when presented with a OSA symptoms.
- Patient access to OSA diagnosis and treatment is inconsistent.

Current experience of treatment

- SATA members were very satisfied with their treatment for OSA from sleep clinics.
- Many patients describe their CPAP as life-changing
- CPAP treatment is associated with difficulties
  - There is discomfort and restriction of having to sleep connected to the machine, also its cleaning and maintenance
  - Use while flying can be an issue as well as the use of the machine in hotels (plug access etc)
- In terms of unmet need no drug therapy exists for OSA
- Partners should be considered to have the same importance as carers

Clinician perspective

Overview

- Significant proportion of patients remain with excessive daytime sleepiness (EDS) with maximal NHS available therapy (in the most cases CPAP therapy) despite being compliant.
- Little or no other options for this group of patients currently.

Unmet need

- OSA not treated pharmacologically (modafinil in rare cases).
- OSA services in the UK are over stretched with diagnosis and treatment of OSA with CPAP (especially post-COVID-19).

Current Treatment

- No clear treatment pathway in the UK, large variation exists based on exposure of cases e.g. larger centres with access to advanced testing who treat patients with sleep conditions like Narcolepsy may treat patient differently to other centres.
- Solriamfetol should be for secondary care specialist clinics (i.e. those able to perform the more advanced testing for EDS on CPAP and are used to titration of medication for sleep disorders).

Evidence from TONES 3

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

*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)

***ICSD-3 is the International Classification of Sleep Disorders

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%)

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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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]

Company 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
	[redacted]	[redacted]	[redacted]	[redacted]
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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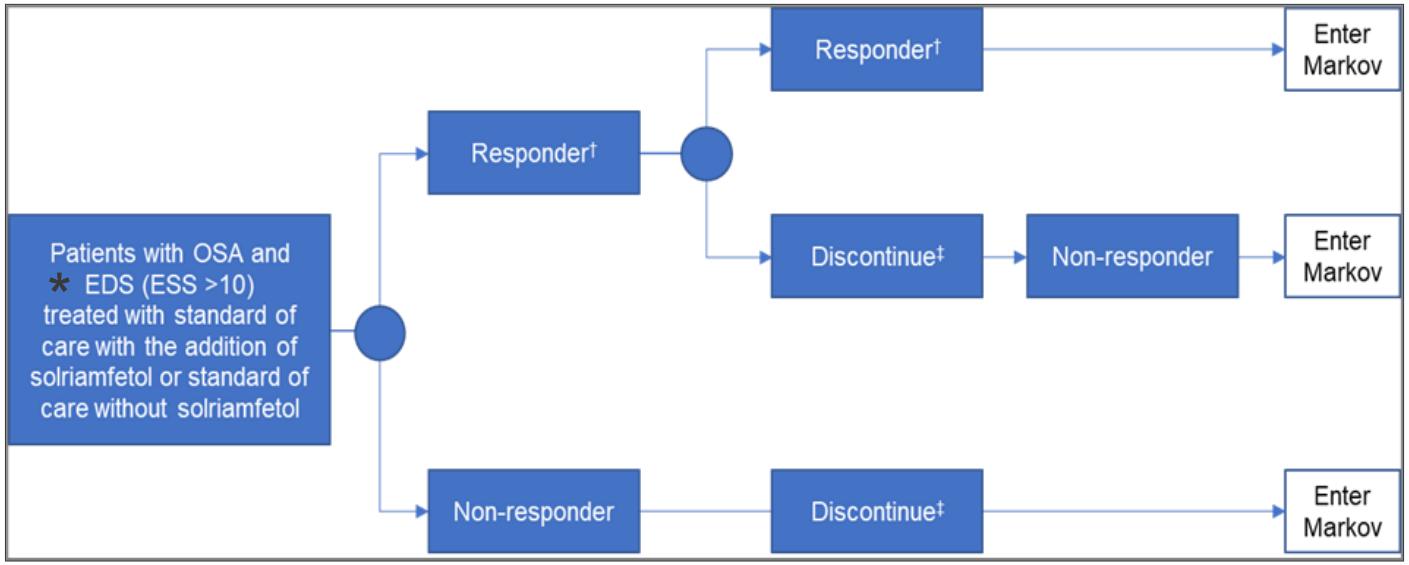
for the open label phase of TONES 5 the changes in ESS are not controlled by a placebo group

Overview of company's Model

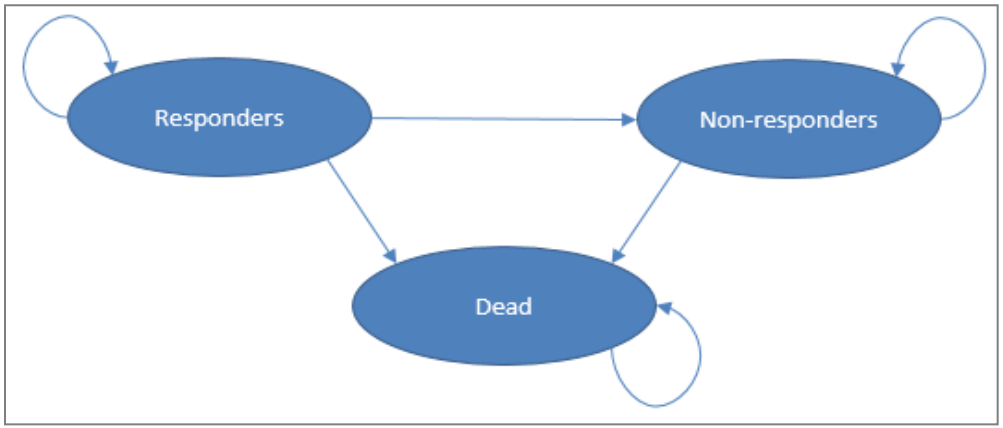
12 WEEK TIME HORIZON

- Decision tree
- 12-week time horizon
- All branches lead into Markov model
- Decision nodes for treatment response



POST 12 WEEKS

- Markov model
- 3 health states
- Annual cycle length
- Lifetime horizon
- Costs, benefits discounted at 3.5% pa
- Half cycle corrections



Input	Data source
Clinical data	• TONES 3
Treatment waning effect	• TONES 5
Utilities	• NHWS analysis mapping ESS to EQ-5D
Costs	• Jazz Pharmaceutical solriamfetol price • PSSRU 2019

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* Company updated base case at engagement to ESS >12

Abbreviations: EDS; Excessive daytime sleepiness; ESS; Epworth sleepiness scale;

Issue 1: Patient compliance with primary OSA therapy

Uncertainty around the impact of Soliramfetol on compliance with primary therapy

Background

ERG suggested compliance with primary OSA therapy **MAY** be compromised if patients prefer the simplicity of a once daily tablet.

Company technical engagement response

The **company** provided Schweitzer et al., a published paper using data from TONES 5 which concluded solriamfetol does not impact primary therapy & UK KOLs have advised that a reduction in compliance with CPAP is not expected.

Stakeholder technical engagement response

Clinician:

- Patients who were already non compliant will likely remain non compliant.
- Those who were compliant will likely remain compliant although some would potentially reduce CPAP usage.

Patient organisation:

- increased non-compliance with CPAP as a direct result of use of this technology could increase overall NHS costs for patients.

ERG views after technical engagement

Schweitzer et al showed little change in primary OSA therapy while using solriamfetol :

- For those using an airway therapy, mean device use at baseline was 90% of nights, 6.6 hours/night, and use ≥50%/night on 90% of nights
- Changes from baseline to week 40 in these 3 measures of compliance were minimal (+0.9%, -0.8 hours, and +6.5%, respectively)
- Substantial missing data and ambiguity about how missing data were analysed

- ***Does solriamfetol affect compliance with primary OSA therapy?***

Issue 2: Model population

Background

- **Company** initially included patients with ESS>10 at baseline, as ESS=10 was considered normal in UK clinical practice.

Company technical engagement response

- **Company** updated its base case using only patients with ESS>12 at baseline
- This group have the greatest clinical need and derive the most benefit from solriamfetol

Stakeholder technical engagement response

Clinician:

- Normal ESS below 9-10 (range ~ 9-12; dependant on age, sex, social class, ethnicity).
- Likely range is 12 – 20 (anyone over 20 may not have EDS just from OSA).

ERG views after technical engagement

- Modelled population ESS > 12 is likely to improve the cost effectiveness of solriamfetol.
- **Increased** uncertainty due to the reduced patient sample size from the trial.
- Questions about this new group fitting with company data from US prescribing patterns
- The ERG updated its base case to a modelled patient population with ESS>12.

Change from baseline ESS for those with an ESS >12 in TONES 3

Drug	N	Proportion of responders (ΔESS from baseline ≥3)	ESS change from baseline in responders
Standard of Care	****	****	****
Solriamfetol 37.5 mg	****	****	****
Solriamfetol 75 mg	****	****	****
Solriamfetol 150 mg	****	****	****

- ***Is it appropriate to restrict the model population to include only patients with more severe EDS (ESS > 12)?***

Issue 3: Definition of treatment response

Uncertainty around the definition of treatment response

Background

- **Company** base case: response is ≥ 3-point reduction in ESS from baseline at 12 weeks. Alternative definitions: ESS of ≥2 or ≥4 points assessed in scenario analyses.
- **ERG** base case response: is of ≥2-point reduction, with scenario analyses of ESS reductions of ≥ 3 and ≥ 4.
- There is considerable variation in the definition of treatment response in clinical practice
- Advice to the **ERG** is that clinicians would consider other factors when assessing treatment effectiveness.

Company technical engagement response

- UK clinical experts agree that ESS is a commonly used factor in decision making around disease severity and response to treatment for EDS in patients with OSA.
- Company base case remains ≥ 3-point reduction in ESS

Stakeholder technical engagement response

Clinician:

- Reduction in ESS of ≥2 is a meaningful response. EDS the most limiting symptom, not easy to monitor or follow.

ERG views after technical engagement

- **ERG** retains base case: treatment response = ESS score reduction of ≥2 points, other estimates are examined in scenario analyses.

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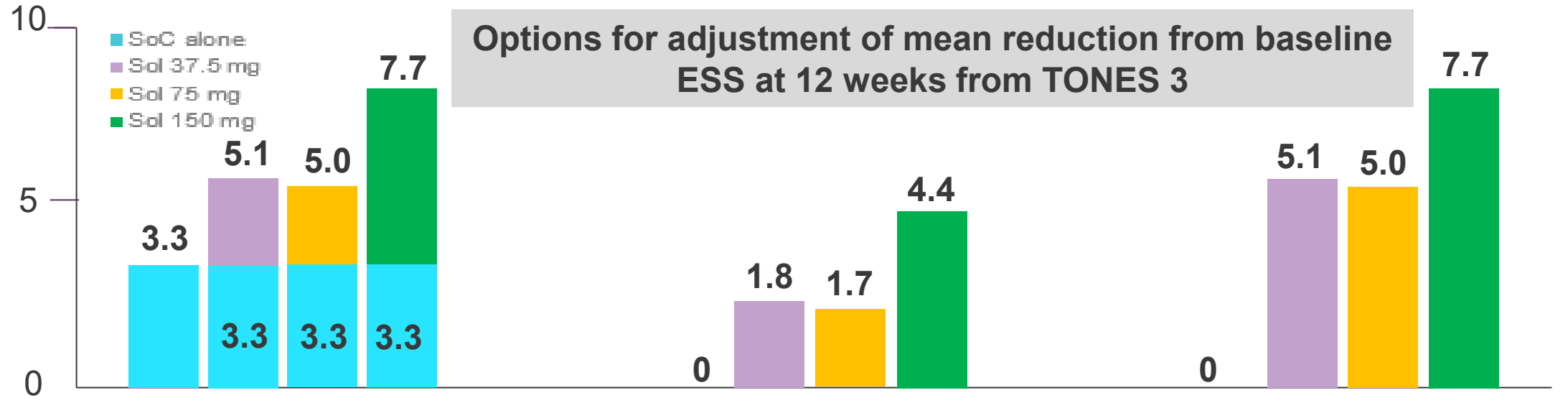
- ***What is the most appropriate definition of treatment response?***

Issue 4: Adjustment of ESS for the placebo effect ('centring')

Uncertainty around the use of centring to adjust for placebo effect

- In TONES 3 a reduction in ESS of 3.3 was observed in placebo arm
- **Company** use centring approach, all patients on standard care remain at baseline ESS
- Adjusts the change from baseline to week 12 in the solriamfetol arms by the mean observed change from baseline to week 12 in the standard care arm.



Regression to the mean (ERG)

- Tendency for extreme values to move closer to the mean when measure repeated over time.
- The same response would be observed in routine practice without the administration of an actual placebo
- Do not adjust trial data

Hawthorne effect (company)

- Placebo response due to act of being observed in trial
- Assumes no response to placebo in routine practice and the placebo response is subtracted from the active treatment response

True placebo (sensitivity analysis)

- Where the placebo response would be seen irrespective of setting
- The response to active treatment and placebo will be the same in routine practice as in the trial.
- If an actual placebo is not administered, no response in routine practice

Issue 4: Adjustment of ESS for the placebo effect ('centring')

Uncertainty around the use of centring to adjust for placebo effect

Company response to engagement

Company reject ERG assumption of regression to the mean:

- Placebo effect not observed in TONES 3 for the Maintenance of Wakefulness Test (MWT)
- Effect of solriamfetol at start of TONES 3, 4 & 5 was rapid, occurring within 1-2 weeks → unlikely to be regression to the mean as this would occur over longer period
- Explored a repeated measures model fitted to ESS data from TONES 3,4 & 5 (combined) on the natural scale → analysis suggested patients on no treatment likely to remain at similar level to baseline
- Real world evidence (qualitative burden of illness study in 15 patients) suggests no regression to the mean
- Plots in baseline ESS vs change from baseline → quantifying regression to the mean from TONES 3 using the methodology suggested by Barnett et al = 0.497 points.

ESS scores in patients from TONES 3 transitioning into TONES 5

Company suggest true placebo is plausible:

- Patients transitioning from TONES 3 to TONES 5 being treated with solriamfetol improve when treatment is unblinded, suggesting further effect from the certainty of knowing their EDS is being managed with active treatment →

Company assume Hawthorne effect in base case (conservative) and true placebo in scenario

Issue 4: Adjustment of ESS for the placebo effect ('centring')

Uncertainty around the use of centring to adjust for placebo effect

ERG views after technical engagement

- Company has not presented sufficient evidence to rule out regression to the mean approach, however true placebo and Hawthorne effect explanations are useful scenarios for committee to consider
- TONES 4 and randomised withdrawal phase of TONES 5 showed improvement in ESS over 2 weeks for blinded placebo but the company has not presented information about within- or between-patient variation in these studies.
- Difficult to interpret results from the company repeated measures analysis → no methods included
- Analysis for patients who progressed to open label solriamfetol from the TONES 3 and 4 trials susceptible to selection bias, as the patients who progressed may not be fully representative of a typical patient population.
- Further information is required to understand the validity and meaning of the company's Barnett formula statistic

[redacted]

This shows that the reduction from baseline ESS is larger for patients who started with a high baseline value

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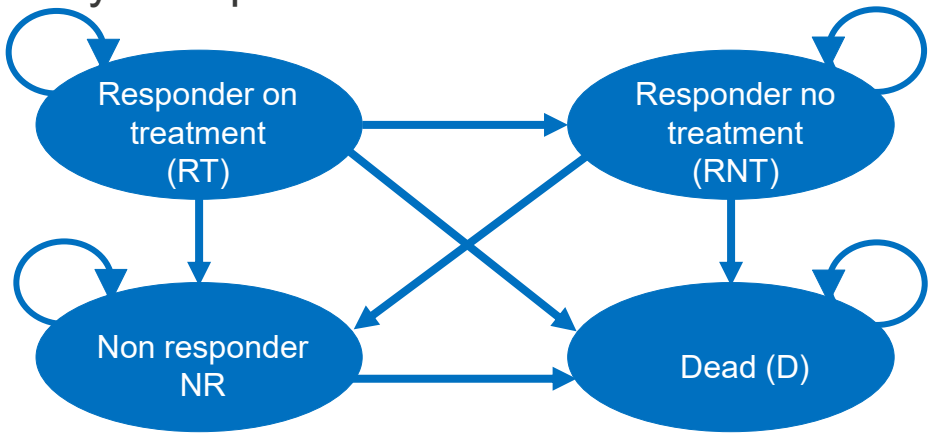
- Is the placebo adjustment used by the company in their modelling appropriate?

Issue 7: Treatment discontinuation and loss of response rates

Uncertainty around the loss of response rate with SoC

Background

- **ERG** noted company had assumed rate of treatment emergent adverse events (TEAE) and loss of response to be the same across all solriamfetol doses, despite evidence from trial suggesting they were dose dependent → Company updated base case after engagement to include dose specific estimates
- Company assumed ESS was constant in SoC arm [see issue 4] → loss of response not an issue
- **ERG** updated the company's base case:
  - assume ESS can vary with SoC (non centred approach) i.e. assume response and loss of response is possible in SoC, without solriamfetol
  - added a fourth health state, Responder No Treatment (RNT), to the company's three-state Markov model → to model possibility of improvement without soliramfetol



Issue 7: Treatment discontinuation and loss of response rates

Uncertainty around the loss of response rate with SoC

Company technical engagement response

- Highlighted potential implausible scenario: solriamfetol treatment can be worse than 'no treatment' with the ERG model
- Despite ERG assumption of RTM [see issue 4] ERGs model allows patients on standard care to discontinue treatment and allow ESS scores to deteriorate → moves away from implied 'true mean'
- Note that the ERG model is highly sensitive to 'no treatment' discontinuation rate

ERG views after technical engagement

- Set the loss of response parameter for standard care equal to the observed rate of discontinuation from solriamfetol due to loss of efficacy from the TONES 3 trial (weighted mean across doses): [redacted] in year 1 and [redacted] per year subsequently.
- agree that it is reasonable to assume that the loss of response rate is likely to be higher with standard care alone than with solriamfetol → explored in scenario analyses
- There is uncertainty over the rate at which patients on standard care with an initial ESS improvement, might be expected to lose this response over time
- Consider that the ERG 4-state version of the model, without adjustment for the placebo effect is an appropriate starting point for the economic analysis.

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- *Are the ERG's assumptions for loss of response in SoC arm appropriate?*
- *Is the ERG 4-state model appropriate?*

Issue 5: Health utility values

Uncertainty around methods used to derive utility values

Background

- **Company** collected EQ-5D-5L in TONES 3 → showed **** between placebo and treatment arms
- **Company** base case used 'mapping' to estimate EQ-5D scores from ESS, used the NHWS mapping study. Alternatives: McDaid et al., TTO were used as scenarios
- **ERG** suggested SF-6D results could have provided important direct information about the utility impact of solriamfetol treatment.
- SF-6D has greater sensitivity than the EQ-5D in OSA

Company technical engagement response

- The NHWS mapping study was completed in line with NICE DSU guidelines
- Mapping has been updated with UK value set for all survey participants

ERG views after technical engagement

- The revision to the NHWS mapping equation for utilities is appropriate.
- Company did not provide SF-6D utility results from TONES 3, as requested. This would have been important supporting evidence for utility impact of solriamfetol

- ***Is the company's mapping approach estimating EQ-5D utility values from ESS using the NHWS mapping study appropriate?***

Issue 6: Partner utilities - *Uncertainty around the use of partner utilities*

Background

- **Company** included partner utilities in a scenario
- **Company** TTO study estimated utility from the perspective of patients and of their partners
- NICE methods guide: perspective on outcomes should include "all direct health effects, whether for patients or for other people".
- **ERG** unclear whether partner utilities should be included → not included in **ERG** base case

Company technical engagement response

- Substantial disutility to partners of a patient with EDS due to OSA, not typically considered in clinical practice
- **Company** believes solriamfetol affects HRQoL beyond patients
- Partner utility gain applied only to TONES 3 participants who were married (66%).
- Including partner utilities reduces the ICERs based on NHWS, McDaid and TTO methods

Stakeholder technical engagement response

Professional organisation:

- Partners should be considered to have the same importance as carers.
- Patient's partner often first becomes aware of symptoms of OSA, and persuades a reluctant patient to seek diagnosis and treatment
- EDS after CPAP is very likely to be observed by the partner

ERG views after technical engagement

- Agree it is important to try to capture the health impact of EDS on partners
- Concerns about high uncertainty over relationship between patient and partner utilities (based on TTO method)

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- ***Should partner utilities be considered?***

Issue 8: The impact of adverse events

Uncertainty around inclusion of hospitalisation costs for SAEs for patients taking solriamfetol

Background

- **Company** model does not include cost for TEAEs not leading to discontinuation: most AEs in TONES 3 were transient and mild/moderate in severity. Assumed 1 GP contact for AEs leading to discontinuation
- **ERG** noted that ***** of serious adverse events (SAEs) in TONES 5 150mg arm led to hospitalisation
- **ERG** included a cost for hospitalised SAEs in their base case.

Company technical engagement response

- Agree that AE management in trial may not apply to English clinical practice
- Conducted analysis of hospital episode statistics and current management of reported AEs
- Suggested ERGs model should not include stroke → stroke occurred in <1% in TONES 5 vs 2.75% of real world patients not on solriamfetol therefore it should not be included in TEAEs
- Believed that monitoring in TONES 5 made it more likely for patients to present to hospital than in a real world setting

ERG views after technical engagement

- Include estimates of hospitalisation costs based on the rates of hospital admissions for SAEs that were considered related to solriamfetol, from TONES 5 (OSA patients)
- Noted the impact of the TEAEs on HRQoL is not modelled (would increase ICER)
- Including costs of hospitalisation has a small impact on ICER, increasing it by <£1000
- Stroke cost was retained in ERG base case

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- *Should the model include costs for serious adverse events that lead to hospitalisation?*

Issue 9: Soliramfetol dose split

Uncertainty around the dose split to be used in UK clinical practice

Background

- Uncertain proportions of 37.5 mg, 75 mg and 150 mg doses of solriamfetol in clinical practice **Company** assumes split of 40/40/20 in base case from KOL feedback
- **Company** has US data for [redacted] split for the 37.5 mg, 75 mg and 150 mg, believes the UK will titrate more slowly
- TONES 5 dose split may not be informative for clinical practice, as participating clinicians were advised to increase dose to the maximum tolerance.
- **ERG** clinical advisor has suggested that some clinicians may want to start patients on the 75 mg dose to reduce the time and resource needed for dose titration

Company technical engagement response

- UK Clinicians report dose split would be determined by response rate, aiming for the lowest effective dose
- They have found no evidence to support the **ERG's** assumption that the dose split could be [redacted].
- UK clinicians experienced in the management of narcolepsy describe taking a cautious approach to titration, "start low" and "slow titration" for other pharmacotherapies used in sleep medicine

ERG views after technical engagement

- In the absence of prescribing evidence or further expert opinion the **ERG** retains the [redacted] dose split in the base case → explores further dose splits in sensitivity analyses

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- What is most appropriate dose split for Solriamfetol?

Innovation and Equality considerations

Innovation

Comments from clinical expert submissions

- Innovative as there is no current treatment in this area so could have substantial benefit (which needs to be offset with the substantial infrastructure improvement needed)

Equalities issues

- No equality issues identified at scoping or technical engagement

- *Is solriamfetol considered innovative? Are there any potential equalities issues?*

Key assumptions in company and ERG analyses

Parameter	Base case		Sensitivity/Scenario analysis
	Company	ERG	
1. CPAP compliance	Not included	Not included	Both explored non-compliance
2. Baseline ESS score	> 12	> 12	Company: ≥ 10, >10
3. Definition of response	≥3 point reduction in ESS	≥2 point reduction in ESS	Company & ERG:≥3, ≥4-point ESS reduction
4. Adjustment for placebo effect	Assume Hawthorne effect. Use 'centring' of IPD	Used uncentred data from TONES 3 (assume RTM) Introduced 4th health state	Company: adjust for 'true placebo effect'
5. HRQOL	ESS to EQ-5D mapping: NHWS	Same as company	Company: McDaid et al & TTO mapping
6. Partner utility values	Not included	Not included	Company: include, using NHWS, McDaid mapping & TTO
7. Response	Dose specific estimates of discontinuation rate for solriamfetol. No loss of response SoC	Dose specific estimates of discontinuation rate for solriamfetol & SoC loss of response	ERG: SoC loss of response 1.5 & 2 x base case value
8. Adverse events	No hospitalisation costs for SAEs	Include hospitalisation costs for SAEs	None
9. Dose splits	40/40/20	[redacted]	Company & ERG: 20/40/40

Cost effectiveness results: Base case

Company's probabilistic results – using list price for solriamfetol

Technologies	Total costs (£)	Total QALYs	Total LYGs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Standard of care	£0	11.877	31.920			
SoC + solriamfetol	£9,855	12.244	31.920	£9,855	0.367	£26,843

ERG deterministic results – using list price for solriamfetol

Technologies	Total costs (£)	Total QALYs	Total LYGs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Standard of care	£0	10.638	30.229	£0	0.000	£0
SoC + solriamfetol	£19,978	10.810	30.229	£19,978	0.171	£116,674

Company cost effectiveness results: Scenario analyses

Deterministic, produced by ERG from company model using list price

Scenario	Related issue	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case	All	£10,889	0.383	£28,453
Compliant to a primary OSA therapy	1	£10,277	0.345	£29,824
Non-compliant to a primary OSA therapy	1	£12,005	0.459	£26,183
Treatment response: reduction in ESS≥2	3	£12,021	0.412	£29,183
[redacted] SOL dose split (ERG base case)	9	£12,645	0.413	£30,635
QoL estimates from TTO analysis	5	£10,889	0.836	£13,025
Partner utilities (NHWS mapping)	6	£10,889	0.524	£20,793
Partner utilities (McDaid mapping)	6	£10,889	0.467	£23,333
Partner utilities (TTO)	6	£10,889	1.144	£9,518

ERG Cost effectiveness results: Base case

Deterministic, produced by ERG using list price

Cumulative analyses	Treat-ment	Costs	QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case (with ERG corrections)	SC	£0	10.033			
	SOL	£10,795	10.412	£10,795	0.379	£28,485
Treatment response: reduction in ESS≥2	SC	£0	10.033			
	SOL	£11,916	10.441	£11,916	0.408	£29,215
SOL dose split: [redacted]	SC	£0	10.033			
	SOL	£13,870	10.474	£13,870	0.441	£31,435
Hospitalisation costs	SC	£0	10.033			
	SOL	£14,324	10.474	£14,324	0.441	£32,465
Removing centring and switching to 4-state model	SC	£0	10.638			
	SOL	£19,978	10.810	£19,978	0.171	£116,674
ERG base case	SC	£0	10.638			
	SOL	£19,978	10.810	£19,978	0.171	£116,674

ERG Cost effectiveness results: Scenario analyses

Deterministic, produced by ERG using list price

Scenario	Related issue	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
ERG base case		£19,978	0.171	£116,674
Compliant patients	1	£18,795	0.145	£129,839
Non-compliant patients	1	£22,293	0.244	£91,508
50%/50% split (compliant/non-compliant)	1	£20,544	0.194	£105,795
Treatment response: reduction in ESS≥3	3	£18,691	0.220	£84,933
Treatment response: reduction in ESS≥4	3	£17,430	0.229	£76,142
With centring and 3-state model	4	£14,324	0.441	£32,465
Without the cost of hospitalisation due to SAEs	8	£19,389	0.171	£113,232
40/40/20 SOL dose split (company base case)	9	£17,763	0.158	£112,401
20/40/40 SOL dose split	9	£24,055	0.222	£108,295

Key issues

ISSUE	KEY QUESTIONS
Issue 1: Potential reduction in patient compliance with primary OSA therapy	• Does solriamfetol affect compliance with primary OSA therapy?
Issue 2: Model population	• Is the ESS level used for selection of patients by the company in their model appropriate?
Issue 3: Definition of treatment response	• What reduction in ESS is most appropriate as definition of treatment response?
Issue 4: Adjustment of ESS for the placebo effect ('centring')	• Is the placebo adjustment used by the company in their modelling appropriate?
Issue 5: Health utility values	• Is the company's mapping approach estimating EQ-5D utility values from ESS using the NHWS mapping study appropriate?
Issue 6: Partner utilities	• Should partner utilities be considered in the analysis?
Issue 7: Treatment discontinuation and loss of response rates	• Are the ERG's assumptions for loss of response in placebo arm appropriate? • Is the ERG 4-state model appropriate?
Issue 8: Adverse events	• Should the model include costs for serious adverse events that lead to hospitalisation?
Issue 9: Solriamfetol dose split	• What is the most appropriate dose split for UK clinical practice for solriamfetol?