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NICE National Institute for Health and Care Excellence

Solriamfetol for treating excessive waketime sleepiness caused by narcolepsy [ID1602]

Lead team presentation

1st appraisal meeting - Committee C

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Company: Jazz Pharmaceuticals

ERG: Southampton Health Technology Assessment Centre (SHTAC)

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Excessive waketime sleepiness (Narcolepsy)

Overview of the condition

- Narcolepsy is a rare, disabling long-term brain disorder that causes a person to fall asleep at inappropriate times. Estimated to affect at least 25,000 people in UK, and usually diagnosed between 20 and 40 years of age.
- In narcolepsy, the brain is unable to regulate sleep and waking patterns normally.
- It can result in **excessive sleepiness**: irrepressible need to sleep, struggle to stay awake and alert, likely to fall asleep during the day (often while eating or talking), regularly napping but wake up feeling unrefreshed, and still sleep for long hours at night.
- Excessive sleepiness caused by narcolepsy can affect many aspects of daily life, including education, employment, driving, relationships, emotional and general health.
- Other symptoms of narcolepsy can include sleep paralysis, excessive dreaming, disturbed nocturnal sleep, sleep attacks (falling asleep suddenly and without warning) and cataplexy (temporary loss of muscle control resulting in weakness and possible collapse [type 1 narcolepsy = presence of cataplexy, type 2 = without cataplexy]).
- Secure Narcolepsy diagnosis made through clinical history and a multiple sleep latency test preceded by overnight polysomnography. More difficult to diagnose without cataplexy (type 2).

Patient and carer perspectives

Narcolepsy UK (including information from Narcolepsy UK charter)

Overview

- Narcolepsy associated with significant physical and mental health comorbidities. It can also impact on family members, relationships and social lives.
- Understanding of condition is poor: Many people have not heard of narcolepsy.

Impact of condition (Narcolepsy UK survey)

- 84% said narcolepsy impacts their mental health/wellbeing, with 79% stating that the condition impacts on their physical health.
- Majority found narcolepsy negatively affects the type of work they can do (82%) and their ability to find (65%), progress within (76%) and keep a job (64%).

Current experience of treatment

- Diagnosis can be delayed. It can be difficult to get GPs to take symptoms seriously. Once referred to neurologists, it can take longer for referral to sleep centres.
- Unmet need: only a few medicines licensed. Getting to right treatment can take years of experimentation/fine-tuning. NHS often limits access to sodium oxybate and pitolisant. Treatment side effects can be severe.
- Advantages of solriamfetol include increasing the choice of medication available and that solriamfetol is less of a stimulant than other treatments.

Professional perspectives

Association of British Neurologists (ABN) submission

Aims of treatment

- Reducing impact of 2 main symptoms: excessive daytime sleepiness and cataplexy.
- Reducing sleepiness/risk of falling asleep at inappropriate situations and reducing cataplexy attacks - improving quality of life (QoL)/ability to do daily activities including work.

Current treatment options

- Limited narcolepsy treatments (with/without cataplexy). Many associated with side effects or contraindicated (particularly cardiac co-morbidities).
- No national guidelines for narcolepsy and no clearly defined treatment pathway. Majority of clinicians in England tend to follow a similar pathway:
  - 1st line: modafinil, 2nd line: dexamfetamine/methylphenidate, 3rd Line: sodium oxybate/pitolisant (3rd line options not available across all centres. Individual funding requests regularly rejected for sodium oxybate).
- Cataplexy treated with antidepressants and sodium oxybate if cataplexy does not respond.
- Solriamfetol likely used 3rd or 4th line (depending on characteristics and co-morbidities).

NICE Clinical expert submission

- Potential for delayed narcolepsy diagnosis (rare condition and may not be Identified easily).
- Solriamfetol an additional treatment option, especially if people are either intolerant or find current medication ineffective. Likely to be better tolerated that some available treatments.
- Measurements such as EQ-5D are insensitive to QoL changes
- Assessment of treatment response predominantly clinical and subjective (questionnaires such as ESS Epworth Sleepiness Scale [ESS] are of limited value).

Solriamfetol (Sunosi, Jazz Pharmaceuticals)

Description of technology	Phenylalanine-derived, second-generation wake-promoting agent. Prevents the reuptake of dopamine and noradrenaline, and indirectly enhances dopaminergic and noradrenergic neurotransmission.
Marketing authorisation (Jan 2020)	Indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy).
Dosage and administration	Available in 2 doses (75mg and 150mg). Recommended starting dose is 75mg. Dose can be titrated up to 150mg after 3-day interval. Administered orally, once daily.
List price	*75mg pack (28) = £177.52 (annual cost = £2,314)* *150mg pack (28) = £248.64 (annual cost = £3,241)*

Treatment Pathway [also issue 1]

Marketing authorisation wording does not require previous treatment before solriamfetol; company position solriamfetol after 1st line modafinil

Association of British Neurologists (ABN) highlights usual pathway and where solriamfetol likely used

1st line — Modafinil

2nd line — Dexamfetamine; Methylphenidate

3rd line — Pitolisant; Sodium Oxybate; **Solriamfetol**

4th line — **Solriamfetol**

ERG clinical advisors and NICE expert stated modafinil standard 1st line. Variable pathway after this.

Company state modafinil considered standard 1st line treatment. Solriamfetol likely used after 1st line modafinil or if modafinil contraindicated/not tolerated

1st line — Modafinil

Following 1st line modafinil, company state there is no clear pathway (based on clinical advice)

Pitolisant; Sodium Oxybate; **Solriamfetol**

Dexamfetamine; Methylphenidate

Costs of treatments for EDS (Narcolepsy)

Treatment		Cost per day (£)	Annual costs (£)
Solriamfetol	75mg	£6.34	£2,314
	150mg	£8.88	£3,241
Pitolisant	18mg	£10.33	£3,770
	36mg	£20.66	£7,540
Sodium Oxybate	4.5mg	£18.00	£6,570
	6mg	£24.00	£9,855
	9mg	£36.00	£13,140
Methylphenidate*	40mg	£1.92	£701
Dexamfetamine*	40mg	£5.30	£1,935
Modafinil**	100mg	£0.11	£40
	200mg	£0.22	£80

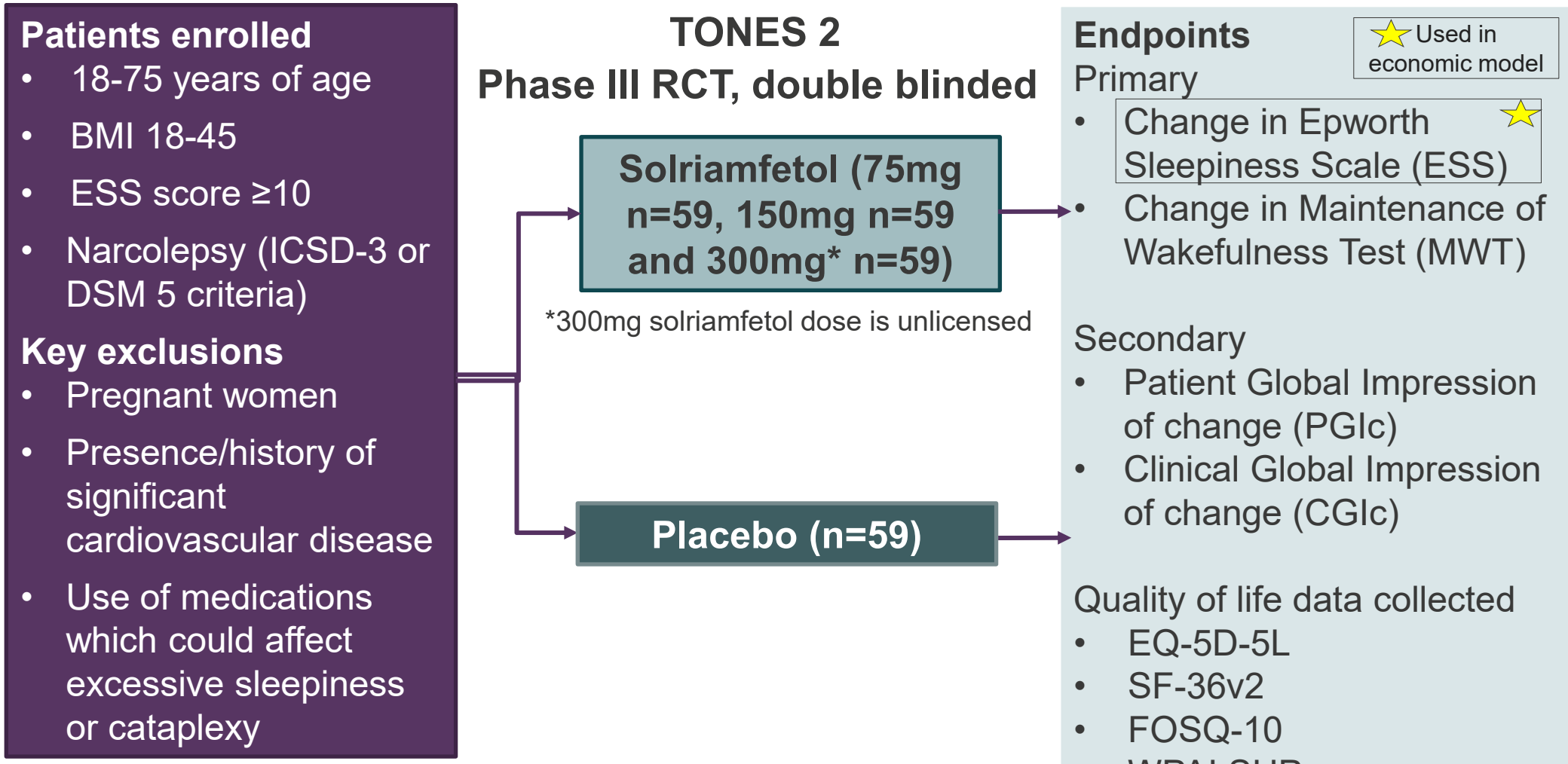
*40mg used in ERG analysis – modified release tablet assumed for methylphenidate
**Modafinil not considered a comparator by company as solriamfetol is positioned after 1st line and not included in analysis

Background

Comparators	NICE scope: modafinil, dexamfetamine, methylphenidate, sodium oxybate and pitolisant • Company position solriamfetol (75mg/150mg) after 1st line modafinil • Comparisons v pitolisant (≤40mg) and sodium oxybate (4.5g/6g/9g) • Comparisons v dexamfetamine, methylphenidate in scenario analysis
Subgroups	None specified in scope • Results by prior modafinil and cataplexy status provided
Clinical trial	TONES 2 (phase III RCT) informs solriamfetol efficacy (v placebo). TONES 1 and TONES 5 = supporting evidence.
Key results	Solriamfetol significantly reduces ESS scores after 12 weeks: 75mg: -2.2 relative to placebo 150mg: -3.8 relative to placebo
Indirect treatment comparison (ITC)	NMA (random-effects) for ESS reduction (at 8wks): solriamfetol 75mg, pitolisant, and sodium oxybate comparisons vs solriamfetol 150mg show 95% credibility intervals cross zero. Dexamfetamine, methylphenidate not included in ITC (no trial data)
Model	Decision tree for 1st 8 weeks and 3 state Markov Model thereafter
Company ICER	£1,352,843 (South West ICER) v pitolisant, dominates sodium oxybate. Scenario analysis v dexamfetamine and methylphenidate, all ICERs >£30,000
Technical team preferred ICER	ERG base case: Solriamfetol dominates both pitolisant and sodium oxybate. ERG scenario analysis v dexamfetamine and methylphenidate: ICERs >£30,000 (all ICERs based on weighted dose splits)

Evidence from TONES 2 trial

Main evidence for solriamfetol comes from TONES 2 which collected data for 12 weeks



Supporting evidence provided from TONES 1 and TONES 5 trials.
Data used to inform some assumptions in economic model

Abbreviations: ESS: Epworth Sleepiness Scale, BMI: Body Mass Index, ICSD-3:International Classification of Sleep Disorders, DSM: Diagnostic and Statistical Manual of Mental Disorders FOSQ-10 functional outcomes of sleep questionnaire, WPAI:SHP: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

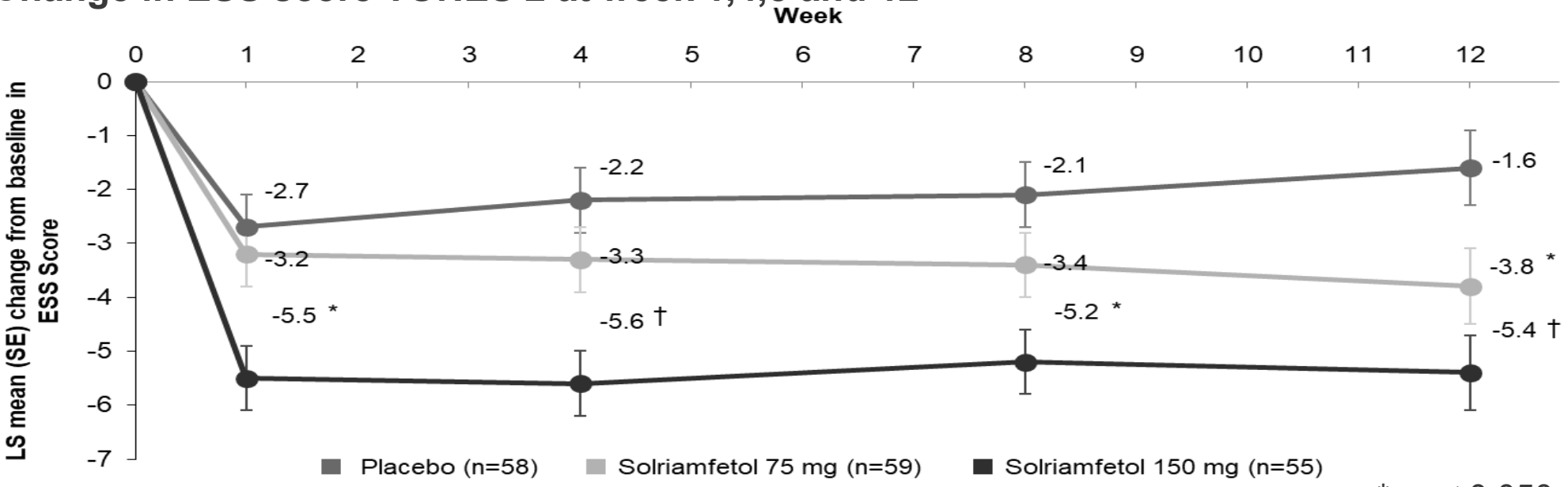
Clinical trial results – TONES 2: ESS

TONES 2 – Phase III RCT ***Solriamfetol compared with placebo (12 week data) – 8 week data used in economic model***			
12-week results	Solriamfetol 75 mg (n=59)	Solriamfetol 150mg (n=55*)	Placebo (n=58*)
Change in ESS score (SE)	-3.8* (0.7)	-5.4** (0.7)	-1.6 (0.7)

- Normal ESS (≤10) scores were achieved by 30.5% and 40.0% of patients in solriamfetol 75 mg and 150 mg groups, compared with 15.5% in the placebo group.

Epworth Sleepiness Scale (ESS): Questionnaire asking *"How likely are you to doze off or fall asleep during the following situations, in contrast to just feeling tired"* – covers 8 situations, with each given a score from 0 (never) to 3 (high chance).

Change in ESS score TONES 2 at week 1,4,8 and 12



* p ≤ 0.050
** p ≤ 0.001

NICE (number of patients in each trial arm, *modified intention to treat)

Abbreviations: ESS: Epworth Sleepiness Scale, SE: standard error

Clinical trial results – TONES 2: Quality of life outcomes

Changes from baseline to week 12 for EQ-5D,5L, EQ-5D VAS, SF36v2 and disease-specific measure FOSQ-10 also collected,

[redacted]

FOSQ-10 score: TONES 2 from baseline to 12 weeks

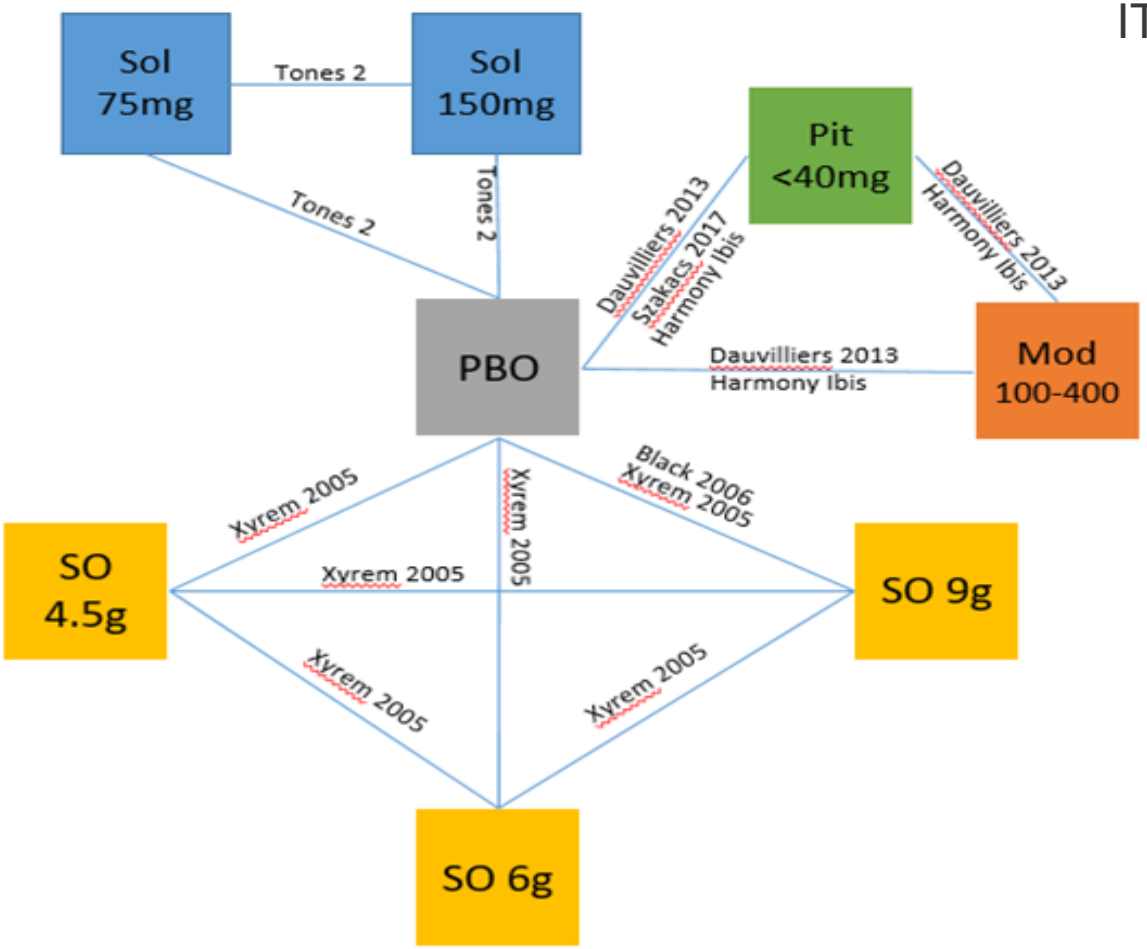
EQ-5D index score: TONES 2 from baseline to 12 weeks

Company model maps from ESS score to EQ-5D index to estimate QALYs

Indirect treatment comparison: Network Meta Analysis (NMA) [Also Issue 4]

TONES 2 only included a placebo comparator - NMA undertaken to compare against comparator treatments

ERG preferred ESS 8-week NMA (company accept ERG revisions)



ITC results (random effects model) – 8 weeks

Relative effects: sol 150mg v treatment	Mean ESS change (95% CI)
Placebo	-3.098 (-6.907, 0.707)
Solriamfetol 75mg	-1.796 (-5.615, 2.019)
Pitolisant ≤40 mg	-0.714 (-5.224, 3.671)
Sodium Oxybate 4.5 g	-2.969 (-8.245, 2.298)
Sodium Oxybate 6 g	-1.964 (-7.248, 3.306)
Sodium Oxybate 9 g	0.654 (-4.048, 5.353)

Results from 8-week ITC show that 95% credibility intervals cross zero for every comparison

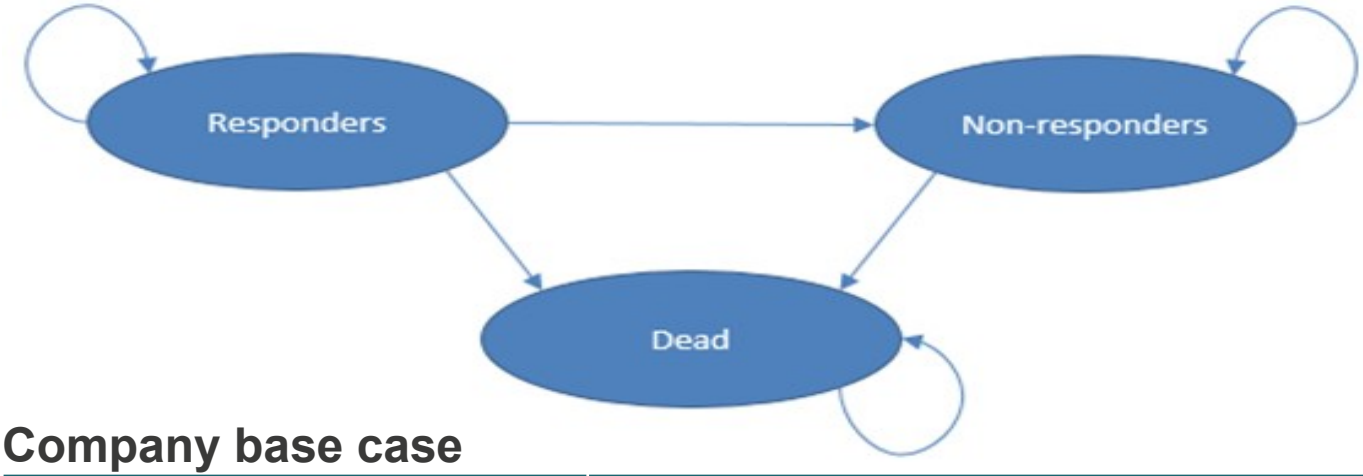
Abbreviations: Sol: Solriamfetol, Pit: Pitolisant, SO: Sodium oxybate, Mod: Modafinil PBO: Placebo

Company's model (Decision-tree and Markov)

Model Structure – Decision tree:
Treatment initiation period (8 weeks)

At 8-weeks % who receive ESS response determined. Withdrawal due to adverse events also estimated. Those whose condition respond go to responder state.

Markov model:
Treatment maintenance period (after 8 weeks)



Model assumptions

- Constant ESS reduction from baseline in responder state.
- ESS returns to baseline after discontinuation.
- No further treatment lines modelled.
- Baseline ESS score ([redacted])
- 4-week cycles. Lifetime horizon
- 3.5% discount rate

Company base case

Parameter	Source
Effectiveness	Mean ESS change (TONES 2) and % of people achieving an ESS threshold reduction. NMA (vs sol 150mg) used to estimate values for comparator therapies. Excess mortality (UK life tables, adjusted), but no treatment effect on length of life assumed.
Utilities	EQ-5D deemed insensitive - Novel mapping algorithm (National Health and Wellness Survey) ESS to EQ-5D: applied to IPD.
Discontinuation: lack of response,adverse events	Lack of ITC data. Informed by TONES 5 data: same rates assumed for all treatments.
Costs and resource use	Only drug costs considered.

Key issues:	Resolved?	*Impact*
Key issues from technical engagement		
Issues 1&2: Treatment Pathway and comparators		*High*
• What is current treatment pathway, when would solriamfetol be used? • What are the relevant comparators for solriamfetol?		
Issue 3: TONES 2 trial population		*?*
• Is TONES 2 generalisable to NHS clinical practice?		
Issue 4: Indirect treatment comparison (ITC)		*?*
• Are results from the indirect treatment comparison robust?		
Issue 5: Subgroup analysis		*Low*
• Is there relevant subgroup analysis that should be considered?		
Issue 6: Estimation of treatment effect		*Low*
• Is efficacy of solriamfetol and comparators captured appropriately?		
Issue 7: Dosing splits		*Low*
• What are the most appropriate dose split assumptions for each treatment?		
Issue 8: Treatment discontinuation		*?*
• Are the modelling assumptions appropriate?		
Issue 9: Resource use		*Low*
• What costs should be included in the analysis?		

NICE

Key	Unresolved	Partially resolved	Resolved/ for brief discussion

Treatment Pathway and comparators [Issues 1&2]

Marketing authorisation wording does not require previous treatment before solriamfetol; company position solriamfetol after 1st line modafinil

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1st line — Modafinil

Following 1st line modafinil, company state there is no clear pathway (based on clinical advice)

Pitolisant; Sodium Oxybate; Solriamfetol; Dexamfetamine; Methylphenidate

No trial evidence for dexamfetamine or methylphenidate in ITC – analysis based on assumed ESS reductions

Treatment Pathway and Comparators [Issues 1&2]

Uncertainty regarding current treatment pathway and appropriate position of solriamfetol.

Background

- NICE scope comparators: modafinil, dexamfetamine, methylphenidate, sodium oxybate, pitolisant. Company positions solriamfetol after modafinil: do not consider modafinil a comparator.
- Company model only 1 treatment line (2nd line).
- Lack of trial evidence for dexamfetamine or methylphenidate - included in scenario analysis (based on assumed ESS reductions).

Company technical engagement response

Treatment Pathway

- Modafinil standard 1st line treatment. Considerable variation post-modafinil.
- Modelling approach reflects available evidence. Modelling treatment sequences not feasible.
- Solriamfetol likely 2nd line therapy, due to efficacy evidence, and license status of alternatives.
- 1st line modafinil not likely to be a treatment effect modifier for subsequent treatments.
- Solriamfetol effective in treating EDS (main symptom) in narcolepsy with/without cataplexy.

Comparators

- Company provide data from Perez-Carbonell et al UK single centre study, % on treatments in this study: Modafinil (54.3%), methylphenidate MR (30.2%), methylphenidate IR (12.9%), dexamfetamine (23.3%) and sodium oxybate (36.2%) across monotherapy/combinations.
- % on treatments in this study high due to inclusion criteria/refractoriness of study population.
- While methylphenidate/dexamfetamine used post modafinil, no available evidence for ITC.

Abbreviations: EDS: Excessive Daytime Sleepiness, ITC: Indirect treatment comparison MR: modified release, IR: instant release

Treatment Pathway and Comparators [Issues 1&2] (2)

Association of British Neurologists (ABN) - technical engagement response

- Modafinil is 1st line treatment. Dexamfetamine or methylphenidate are 2nd line treatments.
- Sodium oxybate or pitolisant are 3rd line options (depending on local availability and patient characteristics) - Pathway may differ by cataplexy status, depending on severity.
- Dexamfetamine and methylphenidate commonly used after modafinil. Efficacy varies. Lack of direct comparative data, but reasonable to include in analysis.
- Solriamfetol likely 3rd/4th line option (influenced by patient characteristics/co-morbidities).
- The more treatments failed, the higher the risk of next treatment not working.
- Some people with cataplexy may have more difficult to treat symptoms.

ERG views after technical engagement

- Agree modafinil used 1st line. Sequences after this less clear, and variability likely.
  - ERG clinical advisors state pitolisant or sodium oxybate sometimes used 2nd line.
- Lack of efficacy data: modelling by treatment line would not change cost or QALY estimates.
- Agree prior modafinil unlikely treatment effect modifier. Company did not comment on possible higher risk EDS not responding to treatment if no response to 1st line modafinil.
- Methylphenidate and dexamfetamine much less expensive (but lack clinical trial data).
- Clinicians report difficulty accessing some treatments, particularly sodium oxybate.
- Additional analysis provided for comparison v methylphenidate and dexamfetamine (including assuming these treatments are as effective as placebo response).

NICE technical team opinion after technical engagement

- Consensus that solriamfetol would be used after modafinil. Lack of consensus of its position after modafinil. Position affects consideration of relevant comparators.

◉ What is the current treatment pathway? Where is the most appropriate position in this pathway for solriamfetol? What are the relevant comparators for solriamfetol?

Issue 3: Generalisability of TONES 2 (source of solriamfetol effectiveness data)

Background: ERG: TONES 2 generally reflects UK narcolepsy population but note location of trial (mainly US/Canada), low % of cataplexy, high % women and a younger population.

TE response company: TONES 2 consistent with UK surveys + UK study (Perez-Carbonell et al)

TE response ABN: low modafinil/stimulant use in TONES 2 may be due to trial location. % with cataplexy slightly lower than UK narcolepsy population. TONES 2 mean baseline ESS similar/slightly lower in UK practice.

ERG views after TE: Clinical advisors agree trial is generalisable (most narcolepsy cases begin in early 20s). Lower % of cataplexy: cataplexy subgroup = no clear difference in results.

Tech team views after TE: TONES 2 appears generalisable, although numbers are small.

Issue 4: Indirect treatment comparison (ESS reduction NMA)

Background: NMA results show credible intervals cross zero for solriamfetol 150mg v each dose of pitolisant/sodium oxybate and 75mg solriamfetol. (random effects model). No trial evidence to include dexamfetamine or methylphenidate.

TE response company: Accept ERG NMA revisions and use of random effects model - Company analyses showed no plausible scenarios result in negative net monetary benefit (NMB) for solriamfetol vs pitolisant or sodium oxybate (fixed effects model – company submission).

TE response ABN: Very difficult to say how uncertain NMA comparisons are. Studies show treatments can be effective, but not possible to say if one treatment is better than another.

ERG views after TE: Random effects NMA has wide credibility intervals, which increases uncertainty and produces a wide ICER range when using these intervals.

Tech team views after TE: ITC limited by small numbers of studies, heterogeneity and inability to stratify by subgroup.

TE = Technical engagement

Issue 5: Subgroup analysis (prior modafinil use and cataplexy status)

Background: ~50% of people in TONES 2 had previous modafinil and ~50% had cataplexy - line of treatment and reasons for not using modafinil unknown. Company provide cost-effectiveness results by cataplexy status and ERG by prior modafinil use.

TE response company: Prior modafinil not likely a treatment effect modifier (TONES 2 not powered to assess). Solriamfetol not thought to affect cataplexy. Subgroup results consistent with base case. Primary focus in clinical practice to reduce EDS. ITC not possible for any subgroup.

TE response ABN:. Solriamfetol appears to provide ESS reduction in people who have had modafinil. Analysis by cataplexy status may be useful. Sodium oxybate treats cataplexy and pitolisant may have a small impact. Dexamfetamine may occasionally have a marginal impact.

ERG views after TE: ERG report cost-effectiveness results by prior modafinil exposure. Results uncertain (low numbers, uncertain modafinil treatment line in TONES 2): cost-effectiveness conclusions unchanged. Unable to replicate company cost-effective results by cataplexy status (no access to IPD). Comparator marketing authorisations suggest some treat EDS + cataplexy

Tech team views after TE: Subgroup analysis useful but limited numbers in data and unable to compare v comparators.

TE = Technical engagement

◉ *Does the committee consider these issues (3-5) resolved? Do these issues add uncertainty to the results*

Estimation of treatment effect [Issue 6]

The economic model uses 8-week NMA data (change in ESS score) applied to individual patient level data (TONES 2 150mg arm) to compare effectiveness of treatments for EDS

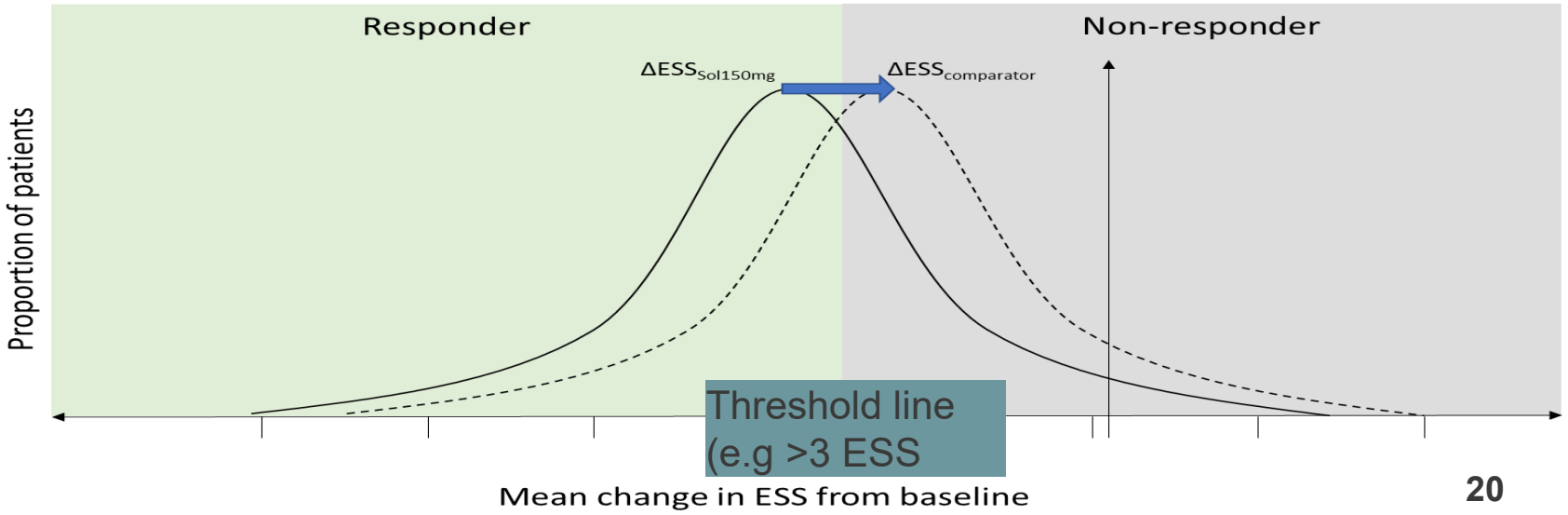
Background

- Efficacy of solriamfetol and comparators in model captured only through changes in ESS from baseline. Company base case: response to treatment = mean ESS score reduction of ≥3.
- ERG consider a mean ESS reduction ≥2 = response in base case, noting other factors used in practice to define response - agreed with use of ESS due to lack of data.
- Response measured at 8-weeks in model to match longest timepoint for comparator trials.
- ERG clinical advisors stated effects of sodium oxybate may take up to 12 weeks to occur.
- Company estimate % on each treatment who experience a response using individual patient data from TONES 2 solriamfetol 150mg arm and results from ESS NMA.
- Constant ESS reduction assumed over time (until discontinuation) if response occurs
- ESS mapped to EQ-5D to estimate QALYs

Change in ESS score relative to 150mg solriamfetol from NMA applied to 150mg IPD, and defined ESS response threshold used to estimate response rate for other treatments.

ERG notes method assumes same distribution of response for all treatments.

Illustration deriving treatment response – company submission figure 17



Estimation of treatment effect [Issue 6]

Company technical engagement responses

- No appropriate alternatives to use of ESS in analysis.
- ESS is a proxy. Appropriate for analysis, considered alongside whether people feel a difference in EDS. Experts state ≥3-point ESS reduction equals response.
- Alternative thresholds (e.g ≥2 or ≥4) did not impact results. 8-week timepoint used due to available data. Alternatives unlikely to change results.

Association of British Neurologists (ABN) technical engagement response

- ESS not most reliable tool but only measure available for comparisons.
- Number of cataplexy attacks and Clinical Global Impression of Change can be used but latter is subject to bias and difficult to compare.
- "whole picture" is considered, including quality of life - difficult to capture this in trials.
- ESS reduction of 3 normally used: however, unknown what reduction is clinically relevant.
- Unclear if treatment effect maintained/constant over time, but reasonable to assume this.
- 8 week timepoint may underestimate sodium oxybate but comparisons still appropriate.

ERG views after technical engagement

- Clinical advisors state ESS change is used in practice alongside self-reported outcomes and MWT seldom used. ERG agrees ESS reduction threshold will vary by patient.
- Constant ESS reduction assumption when EDS responds to treatment is appropriate.
- 8-week timepoint appropriate (based on available comparator data) but may underestimate sodium oxybate effectiveness. Cost-effectiveness estimate not sensitive to timepoint used.

NICE technical team opinion after technical engagement

- Likely use of ESS alone to estimate treatment effect fails to fully reflect clinical practice and adds uncertainty. However, there is no alternative measure available.

◉ *Is ESS reduction an appropriate measure? Is the 8-week timepoint used in the NMA appropriate? Is the company's method to estimate response rates appropriate?*

Issue 7: Dosing splits (treatments are available in different doses)

Background: company assumed 50/50 (75mg/150mg) solriamfetol dose split - US data. Comparator assumptions: pitolisant 18mg (33%), 36mg (67%), sodium oxybate (33% on 4.5 ,6 and 9mg) - ERG: assume 10/90 solriamfetol dose split (clinical advice), consider company comparator treatment dose split reasonable (sensitivity analysis provided).

TE response company: Data from France and Germany show [redacted] and [redacted] dose splits: updated analysis using these splits do not alter cost-effectiveness results. ERG sensitivity analysis: solriamfetol cost-effective under all dosing assumptions (v pitolisant or sodium oxybate).

TE response ABN: Higher dose likely tried (to test tolerance) if response achieved with lower dose. Unknown what % on higher dose, solriamfetol not used currently (rough estimate ~75%). Dose split between higher/lower doses likely the same for all treatments.

ERG views after TE: New prescribing data provided by company useful. Cost-effectiveness results in general not sensitive to other dosing assumptions (ERG sensitivity analysis).

Tech team views after TE: Cost-effectiveness conclusions are not sensitive to dose split

Issue 8: Treatment discontinuation (lack of response or adverse events)

Background: Company assume same long term discontinuation rates (TONES 5) for treatments due to lack of response/adverse events. ERG considered assumptions reasonable (lack of data).

TE response company: Solriamfetol cost-effective option under various discontinuation rates. ITC implies merit of cost minimisation analysis: solriamfetol lower costs vs pitolisant and sodium oxybate. Updated analysis using adverse event NMA does not change results.

TE response ABN: Some people discontinue treatment quicker: this applies for all treatments.

ERG views after TE: Support base case assumption of same discontinuation rate for all treatments (lack of data and high uncertainty in company's additional discontinuation analysis)

Tech team views after TE: Company assumptions appear reasonable given lack of data

Issue 9: Resource use

Background: Company only include drug acquisition costs. ERG includes consultant appointments and hospitalisation costs (for managing serious adverse events).

TE response company: Absolute incidence of serious adverse events low for solriamfetol. Most adverse events occur early, are mild and resolve quickly. ERG estimates hospitalisation costs (3.5 days) due to sleep disorders, rather than adverse events and biases estimates upwards.

TE response ABN: Number of appointments does not change depending on treatment - usually no free clinic spots. People who are not well may require more frequent assistance by phone. People with poorly controlled narcolepsy may need increased healthcare.

ERG views after TE: Follow-up may differ for those with more/less controlled symptoms (clinical advice to ERG): appropriate to include these costs. Agree incidence of serious adverse events is low, inclusion of hospitalisation costs an appropriate conservative assumption. ERG cost assumptions have minor impact on cost-effectiveness results.

Tech team views after TE: Cost-effectiveness conclusions not sensitive to resource use assumptions.

◉ *Does the committee consider these issues (7-9) resolved? Do these issues add uncertainty to the results?*

Equality considerations and innovation

Innovation

Comments from submissions

- Not innovative but an additional therapy in management of narcolepsy.
- Slightly different mode of action to current options and may be an important addition.
- Solriamfetol has a selective mechanism of action, low abuse potential, convenient dosing schedule and extended duration of response.

Equalities issues

- One comment stated some people experiencing EDS may be have borderline narcolepsy as tests not definitive where cataplexy not present. Typically referred to as Narcolepsy Type 2, some may be referred to/diagnosed with Idiopathic Hypersomnia.
  - The technical team notes that the marketing authorisation does not specify narcolepsy type and includes the narcolepsy type 2 population.

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

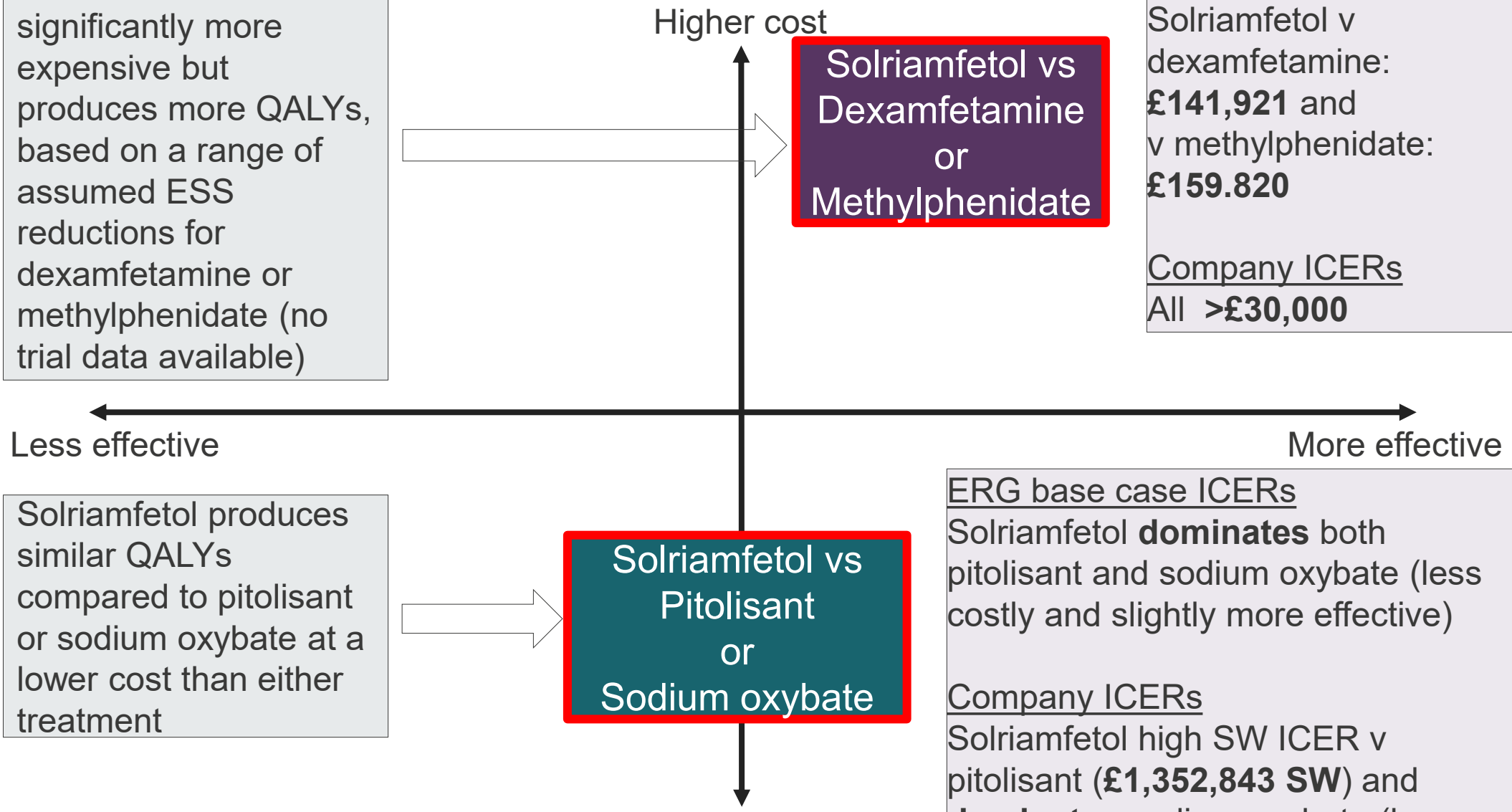
Key assumptions in company and ERG analyses

Following technical engagement, the ERG and company base cases both use the ERG's NMA and random effects model for the indirect treatment comparison.

Parameter	Base case		Sensitivity/scenario analysis
	Company	ERG	
Population	TONES 2 150mg arm.	Full TONES 2 population.	Subgroups: prior modafinil, cataplexy status.
Treatment pathway + Comparators	Positioned after 1st line Modafinil – comparisons vs pitolisant and sodium oxybate.	Same as company.	Comparison vs dexamfetamine and methylphenidate (assumed ESS reductions).
NMA and subgroups	ERG NMA and random effect model. 8-week timepoint.	Same as company.	12-week timepoint. NMA could not be stratified by subgroups.
Definition of response	≥3 ESS reduction	≥2 ESS reduction.	≥2 to ≥4 ESS reduction thresholds used.
HR-QoL	ESS to EQ-5D mapping: NWHS.	Same as company.	McDaid et al mapping (TA139).
Assumed dose splits	Sol 75/150mg : [redacted] (updated, French data) Pit: 18mg 33%, 36mg 66% Sod: 4.5g/6g/9g: 33% each	Sol: 10%/90% dose split	German dosing data, alternative dose splits tested
Model assumptions	Constant ESS reduction from baseline over time. Treatment discontinuation rates from TONES 5 (all treatments).	Same as company.	Alternative discontinuation rates tested
Resource use	Only drug acquisition costs considered.	Drug and healthcare resource costs.	Frequency of consultations varied.

Appropriate comparator(s)?

Solfriamfetol significantly more expensive but produces more QALYs, based on a range of assumed ESS reductions for dexamfetamine or methylphenidate (no trial data available)



ERG scenario ICERs
Solriamfetol v dexamfetamine: **£141,921** and
v methylphenidate: **£159.820**

Company ICERs
All **>£30,000**

Solriamfetol produces similar QALYs compared to pitolisant or sodium oxybate at a lower cost than either treatment

ERG base case ICERs
Solriamfetol **dominates** both pitolisant and sodium oxybate (less costly and slightly more effective)

Company ICERs
Solriamfetol high SW ICER v pitolisant (**£1,352,843 SW**) and **dominates** sodium oxybate (less costly and slightly more effective)

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Cost-effectiveness results: Base case

Company Base Case: Based on French dosing split data and updated ERG ITC – PSA**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER	Solriamfetol pairwise
Solriamfetol	£8,322	13.368			Reference	Reference
Pitolisant	£19,242	13.376	£10,920	0.008	**£1,352,843**	**£1,352,843 SW**
Sodium oxybate	£25,860	13.336	£6,618	-0.040	**Dominated**	**Dominates**

****ERG**: Bootstrapping method applied in company's PSA underestimates uncertainty (re-samples should be same size as the original dataset: company use 5,000 resamples).

ERG Base Case – deterministic analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER	Solriamfetol pairwise
Solriamfetol	£23,086	13.547			Reference	Reference
Pitolisant	£31,169	13.515	£8,083	-0.032	**Dominated**	**Dominates**
Sodium oxybate	£42,309	13.483	£11,150	-0.064	**Dominated**	**Dominates**

*SW: South West quadrant (solriamfetol less costly and less effective than comparator)

Cost-effectiveness results scenario analyses:
Solriamfetol v dexamfetamine/methylphenidate

ERG scenario analysis – including dexamfetamine and methylphenidate as comparators

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER	Solriamfetol Pairwise
Methylphenidate*	£1,676	13.413	Reference	Reference	Reference	£159,820
Dexamfetamine*	£4,074	13.413	£2,398	0	Dominated	£141,921
Solriamfetol	£23,086	13.547	£19,012	0.134	£159,820	Reference
Pitolisant	£31,169	13.515	£8,083	-0.032	Dominated	Dominant
Sodium oxybate	£42,309	13.483	£11,410	-0.032	Dominated	Dominant

*Dexamfetamine (40mg) and methylphenidate MR (40mg) (assumed -3 ESS reduction relative to solriamfetol 150mg due to lack of trial data)

ERG also ran scenario analysis estimating solriamfetol cost-effectiveness v methylphenidate and dexamphetamine under “extreme/optimistic” assumptions (based on company base case).

ERG scenario analysis – dexamfetamine and methylphenidate equal to placebo response

v dexamfetamine/ methylphenidate	ICER sol v dexam	ICER sol v methyl
Dexam/methyl equal to placebo (-3.098**)	£41,689	£53,003
lower 95% placebo credible interval (-6.907)**	£33,160	£35,620

ERG notes that scenario analysis also assumes no differences in adverse events – may not be realistic.
** assumed difference in ESS reduction v solriamfetol 150mg)

Company Scenario analysis vs dexamfetamine and methylphenidate: Range of analysis involving various doses. All ICER estimates >£30,000 for solriamfetol based on assumed ESS reductions (Tables 81 & 84 company submission)

Cost-effectiveness results: Sensitivity/scenario analysis

Company scenario/sensitivity analysis: Pairwise

Parameter	ICER sol v Pit	ICER sol v sod
German dose split data	£800,806 (SW)	Dominant
Population with cataplexy	£1,028,258 (SW)	Dominant
Population without cataplexy	£1,479,712 (SW)	Dominant
Discontinuation rates from TEAE ITC	Dominant	£217,915 (SW)
Comparator discontinuation rates halved	£145,063 (SW)	Dominant
Comparator discontinuation doubled	Dominant	Dominant

ERG scenario/sensitivity analysis: Pairwise (based on company revised based case)

Parameter	ICER sol v Pit	ICER sol v sod
Population with prior modafinil	£5,559,116 (SW)	Dominant
Population without prior modafinil	£682,244 (SW)	Dominant
ESS response defined ≥2 points	Dominant	Dominant
ESS response defined ≥4 points	£1,070,764 (SW)	Dominant

Sol: Solriamfetol, Pit: Pitolisant, Sod: Sodium Oxybate

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*SW: South West quadrant (solriamfetol less costly and less effective than comparator)

Key issues:	Resolved?	Impact
Key issues from technical engagement		
Issues 1&2: Treatment Pathway and comparators		*High*
• What is current treatment pathway, when would solriamfetol be used? • What are the relevant comparators for solriamfetol?		
Issue 3: TONES 2 trial population		*?*
• Is TONES 2 generalisable to NHS clinical practice?		
Issue 4: Indirect treatment comparison (ITC)		*?*
• Are results from the indirect treatment comparison robust?		
Issue 5: Subgroup analysis		*Low*
• Is there relevant subgroup analysis that should be considered?		
Issue 6: Estimation of treatment effect		*Low*
• Is efficacy of solriamfetol and comparators captured appropriately?		
Issue 7: Dosing splits		*Low*
• What are the most appropriate dose split assumptions for each treatment?		
Issue 8: Treatment discontinuation		*?*
• Are the modelling assumptions appropriate?		
Issue 9: Resource use		*Low*
• What costs should be included in the analysis?		

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Key	Unresolved	Partially resolved	Resolved/ for brief discussion