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Evidence Review Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Solriamfetol for treating excessive sleepiness caused by narcolepsy

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TABLE OF CONTENTS

1 Executive Summary 10
1.1 Critique of the decision problem in the company's submission 10
1.2 Summary of the key issues in the clinical effectiveness evidence 10
1.3 Summary of the key issues in the cost effectiveness evidence 11
1.4 Summary of ERG's preferred assumptions and resulting ICER 16
1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG 17
2 INTRODUCTION AND BACKGROUND 18
2.1 Introduction 18
2.2 Background 18
2.3 Critique of company's definition of decision problem 21
3 CLINICAL EFFECTIVENESS 24
3.1 Critique of the methods of review(s) 24
3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these) 26
3.3 Critique of studies identified and included in the indirect comparison and/or multiple treatment comparison 52
3.4 Critique of the indirect comparison and/or multiple treatment comparison. 58
3.5 Results from the indirect comparison 64
3.6 Additional work on clinical effectiveness undertaken by the ERG 68
3.7 Conclusions of the clinical effectiveness section 72
4 COST EFFECTIVENESS 75
4.1 ERG comment on company's review of cost-effectiveness evidence 75
4.2 Summary and critique of the company's submitted economic evaluation by the ERG 76
5 COST EFFECTIVENESS RESULTS 109
5.1 Company's cost effectiveness results 109
5.2 Company's sensitivity analyses 112
5.3 Subgroup analysis 116
5.4 Model validation and face validity check 116
6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES 123
6.1 ERG's preferred assumptions 123
6.2 Scenario analyses undertaken by the ERG 124
6.3 Conclusions of the cost effectiveness section 126
7 END OF LIFE 126
8 REFERENCES 127
9 APPENDICES 133

LIST OF TABLES

Table 1 ICER resulting from ERG's preferred assumptions 17
Table 2 Summary of decision problem 21
Table 3 ERG appraisal of systematic review methods 24
Table 4 Characteristics of the three TONES trials 27
Table 5 ERG Review of Baseline Characteristics of Participants in TONES trials ... 29
Table 6 Quality assessment results for parallel group RCTs (TONES 2 and TONES 1) 31
Table 7 Outcome measures: TONES 2 33
Table 8 Efficacy outcomes measured: TONES 5 36

Table 9 Contribution of outcome data to company's base case economic model 37
Table 10 Summary of statistical methods used in the TONES studies 38
Table 11 Effects of solriamfetol on change in ESS compared to placebo at week 8 42
Table 12 TONES 2: HRQoL endpoints (mITT Population) 43
Table 13 TONES 5 Change in mean ESS scores from baseline for patients with narcolepsy for the solriamfetol 75 mg and 150 mg dose (Safety population) 46
Table 14 Subgroup analysis in TONES 2: cataplexy status 48
Table 15 Adverse events reported in TONES trials in narcolepsy patients 49
Table 16 Adverse events of special interest 50
Table 17 Included studies/citations for the ITC from the RCT search 53
Table 18 ESS week 8 relative effects (as mean difference) and absolute effects 65
Table 19 Scenario: ESS week 8 relative effects (as mean difference) and absolute effects 67
Table 20 ESS week 8 and week 12 relative effects (as mean difference) 70
Table 21 Discontinuations due to TEAEs (as relative risk) 71
Table 22 Incidence of serious TEAEs (as relative risk) 72
Table 23 Features of UK economic analyses that informed the company analysis .. 75
Table 24 NICE reference case checklist 77
Table 25 Base case estimates of response, mean ESS and utility 79
Table 26. Baseline characteristics for the modelled cohort 85
Table 27 UK EQ-5D-3L and SF-6D population norms 93
Table 28 Utility estimates from literature: EQ-5D based 94
Table 29 Utility estimates from literature: SF-36 based 95
Table 30 Frequency of outpatient appointments 107
Table 31 Proportion of patients hospitalised per model cycle 108
Table 32 HRG codes 108
Table 33 Company base case results by dose based on bootstrap sampling 110
Table 34 Company base case results for combined doses with bootstrap sampling 110
Table 35 Company base case results for separate doses based on raw IPD 111
Table 36 Company base case results for combined doses based on the raw IPD. 112
Table 37 CS Results of univariate analysis: solriamfetol vs pitolisant 113
Table 38 Results of univariate analysis: solriamfetol vs sodium oxybate 113
Table 39 Corrections to the unit costs of the comparator treatments 117
Table 40 Summary of key issues in the company's analysis 118
Table 41 Cumulative change from the company to ERG base case 123
Table 42 ERG scenario analyses 124
Table 43 ESS week 8 relative effects (as mean difference) and absolute effects .. 143
Table 44 Mechanisms of action and dosage 143
Table 45 Drug acquisition costs used in the company's base case analysis 145
Table 46 Pitolisant titration, maintenance dosing and costs assumed in the company's model 145
Table 47 Drug acquisition costs used in the company's sensitivity analysis for dexamfetamine 146
Table 48 Drug acquisition costs used in the company's sensitivity analysis for methylphenidate 146
Table 49 Primary care physician visits in the open label phase of TONES 5 (safety population) 147
Table 50 Sleep Specialist visits in the open label phase of TONES 5 (safety population) 147

Table 51 Psychiatrist visits in the open label phase of TONES 5 (safety population) 147
Table 52 Ear Nose and Throat Specialist visits in the open label phase of TONES 5 (safety population)..... 147
Table 53 Other Type of Specialist visits in the open label phase of TONES 5 (safety population) 147
Table 54 Health care costs incurred in the open label phase of TONES 5 (safety population) 148
Table 55 AE-related hospitalisation of patients receiving solriamfetol 75 mg or 150 mg in TONES 5 148

LIST OF FIGURES

Figure 1 ESS 8-week NMA network diagram 60
Figure 2 ESS 8-week NMA scenario: impact of concomitant therapy on sodium oxybate network diagram 66
Figure 3 ERG's ESS week-8 network including modafinil and the Harmony Ibis trial 69
Figure 4 ERG's Serious TEAE network..... 69
Figure 5 Treatment initiation – Decision tree..... 78
Figure 6 Maintenance treatment – Markov model 78
Figure 7 Transformation of IPD for comparator..... 89
Figure 8 FOSQ change from baseline, TONES 2 mITT population..... 97
Figure 9 EQ-5D index score change from baseline, TONES 2 mITT population..... 97
Figure 10 SF-36 PCS change from baseline, TONES 2 mITT population..... 98
Figure 11 SF-36 MCS change from baseline, TONES 2 mITT population 98
Figure 12 ESS 8-week NMA scenario: impact of separating pitolisant doses 142

LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AIC	Academic in confidence
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
CGI-c	Clinical Global Impression of change
CGI-s	Clinical Global Impression of severity
CI	Confidence interval
CIC	Commercial in confidence
CPAP	Continuous positive airway pressure
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DIC	Deviance Information Criterion
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSU	Decision Support Unit
DVLA	Driving and Vehicle Licence Authority
EDS	Excessive daytime sleepiness
EFNS	European Federation Neurological Societies
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ESS	Epworth Sleepiness Scale
ERG	Evidence Review Group
FOSQ-10	Functional Outcomes of Sleep Questionnaire short version
HCP	Healthcare practitioner
HRG	Healthcare Resource Group

HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICSD	International Classification of Sleep Disorders
IPD	Individual patient level data
ITC	Indirect treatment comparison
ITT	Intent to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KOL	Key opinion leader
LOCF	Last observation carried forward
LS	Least squares
MCS	Mental component summary
mITT	Modified intent to treat
MMRM	Mixed-effect model with repeated measures
MWT	Maintenance of Wakefulness Test
MWT20	20-minute Maintenance of Wakefulness Test
MWT40	40-minute Maintenance of Wakefulness Test
NHS	National Health Service
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NR	Not reported
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea hypopnoea syndrome
PCS	Physical component summary
PGI-c	Patient Global Impression of change
PSA	Probabilistic sensitivity analysis
PSG	Polysomnography
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
REM	Rapid eye movement
RR	Relative risk/risk ratio
RTA	Road traffic accident

SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36(v2)	Short-Form 36-Item Health Survey (version 2)
SF-6D	6-Dimension Short Form 36 Health Survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA139	NICE TA139 CPAP for the treatment of OSAHS
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TONES	Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WHO	World Health Organisation
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1 Executive Summary

1.1 Critique of the decision problem in the company's submission

The company's decision problem deviates from the final NICE scope in the following respects:

- Population: the company have restricted the population in their decision problem to adult narcolepsy patients with excessive daytime sleepiness (EDS) who have failed, or who are intolerant to modafinil, or for whom modafinil is contraindicated. Clinical advice to the Evidence Review Group (ERG) supports the continued use of modafinil as a first-line treatment and the positioning of solriamfetol as a second-line treatment option.
- Comparators: as a consequence of the company's decision to position solriamfetol as a second-line therapy after modafinil, modafinil is excluded as a comparator.

The intervention and outcomes in the company's decision problem align with the NICE scope and there were no subgroups listed as being of interest in the NICE scope.

1.2 Summary of the key issues in the clinical effectiveness evidence

The ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be of a sufficiently good standard to inform this Single Technology Appraisal (STA) (Section 3.1 of this ERG report).

The key clinical effectiveness evidence for solriamfetol in a population of adults with narcolepsy comes from the company's pivotal 12-week multicentre phase III randomised controlled trial (RCT) named TONES 2. TONES 2 was judged to be at low risk of bias. Three of the four arms of this RCT are relevant to this STA: placebo; solriamfetol 75 mg once daily; and solriamfetol 150 mg once daily (safety population, [redacted] in each arm). The dose of solriamfetol in the fourth arm (300 mg once daily) is not licenced and hence is not considered in the Company Submission (CS) or the ERG report (Section 3.2.1 of this ERG report).

The co-primary efficacy outcomes for TONES 2 were the change in Epworth Sleepiness Score (ESS) from baseline to week 12 and the change in Maintenance of Wakefulness Test 40 minutes (MWT40) from baseline to week 12. The mean improvement with solriamfetol in ESS score at week 12 was clinically significant and the mean differences relative to placebo

were statistically significant for both solriamfetol doses. For the MWT40, a statistically significant improvement relative to placebo was observed at week 12 for the solriamfetol 150 mg dose but not for the 75 mg dose. The effectiveness outcome used in the economic model was ESS change from baseline at 8 weeks (a secondary outcome in TONES 2) and a statistically significant mean difference in ESS relative to placebo occurred only for the 150 mg solriamfetol dose at this time point. There were [redacted] for either solriamfetol dose in comparison to placebo in terms of HRQoL including EQ VAS, EQ-5D-5L Index, SF36v2, and FOSQ-10 (Section 3.2.5 of this ERG report).

There were no head-to-head comparisons of solriamfetol against any of the comparators listed in the NICE scope, so the company carried out network meta-analyses (NMAs) to indirectly estimate ESS and other outcomes for solriamfetol relative to pitolisant and sodium oxybate. No evidence that could be used in an indirect comparison was identified for the comparators dexamphetamine or methyphenidate (Section 3.3 of this ERG report).

The NMA used to directly inform data inputs to the company's base case economic model is the ESS change from baseline at 8 weeks which incorporated data from five trials. The ERG believes a sixth trial should have been included and that modafinil arms from two trials should also have been included as they added to network connectivity and allowed an assessment of consistency in the placebo-pitolisant-modafinil loop. The fixed-effect model favoured by the company shows that solriamfetol 150 mg provides an improvement in ESS relative to placebo, solriamfetol 75 mg and sodium oxybate at a dose of 4.5 g. The ERG favours the random-effects model where credible intervals cross zero for every comparison (Section 3.5 of this ERG report). The ERG ran their own analysis, including the additional trial, including modafinil arms from two trials and correcting any data input errors identified. The ERG's results are very similar to the results presented by the company (Section 3.6 of this ERG report).

1.3 Summary of the key issues in the cost effectiveness evidence

Model structure and assumptions

The general structure of the company's model is appropriate for the decision problem, but there are some issues related to model assumptions:

- Treatment response is defined purely in terms of reduction in ESS score from baseline (≥3 points). However, clinicians have suggested that they would want to

consider additional factors, such as impact quality of life, when making this assessment.

- There is uncertainty over the timing of response assessment. We think that the company's argument for using the 8-week time point in the base case is reasonable. Although 12 weeks was the primary endpoint in TONES 2, using 12 weeks would introduce inconsistency with data from comparator trials (which were only available up to 8 weeks). However, this may introduce bias against sodium oxybate, which can take up to 3 months before an improvement is seen. ESS is likely to be similar at 4, 8 and 12 weeks for other comparators.
- The model includes several assumptions for simplicity or due to a lack of data. These include the omission of further lines of therapy after discontinuation of the second-line treatments, which does not reflect UK clinical practice. And, in the absence of long-term data on outcomes and persistence of treatment effects, it is assumed that medication doses do not change after the treatment initiation period; that mean ESS does not change as patients age; and that treatments do not affect survival. Such assumptions may be difficult to avoid, but they are associated with uncertainty that is not reflected in the sensitivity and scenario analyses.
- The model uses a lifetime horizon but is not sensitive to the use of a shorter time horizon. However, the lifetime horizon results are subject to uncertainty due to various assumptions used for extrapolation.

Representativeness of the population

There is some uncertainty whether the clinical trials are reflective of people in the UK with narcolepsy. In particular, the model relies on individual-level data for a small sample of patients who were randomised to the 150 mg dose in the TONES 2 trial. This may introduce bias if this sample is unrepresentative.

The company present a subgroup analysis for patients who have previously had modafinil. This is potentially important, because it aligns with targeted use of solriamfetol after failure or intolerance/contraindication to modafinil. However, the subgroup analysis restricts the sample size from the TONES 2 trial, and so may not be robust.

Comparators

The company include pitolisant and sodium oxybate as comparators in their base case economic analysis. We agree with the exclusion of modafinil because of its established place as first-line therapy. Dexamfetamine and methylphenidate are only included in scenario analyses. This is reasonable because, although these drugs are used for

narcolepsy and have a low acquisition cost, there is a lack of suitable clinical data to assess their effects relative to solriamfetol and the other comparators.

Dose mix

The company present cost-effectiveness results for the separate doses of solriamfetol (75 mg and 150 mg) and sodium oxybate (4.5 g, 6 g and 9 g) as well as for combined doses. We think the combined-dose analyses will be more useful for decision-making because individuals can, and do, have their dose adjusted to balance treatment effectiveness and the risk of side effects. The company assume an equal split between the available doses in their combined-dose analyses, but there is uncertainty over the dose mixes that would be used in routine NHS practice. This has implications for the pooled costs and effects across the dose levels.

Clinical effectiveness

The main clinical outcomes that drive the economic model are mean differences in change from baseline ESS (ΔESS) over the 8-week treatment-initiation period from the indirect treatment comparaison (ITC) analysis. These results are used together with individual patient data (IPD) to estimate the proportion of responders (ΔESS≥3) to each treatment, the mean ESS for responders and mean ESS for non-responders. The IPD dataset is comprised of patients randomised to 150 mg solriamfetol in the TONES 2 trial with EDS (n=[redacted]).

The ERG considers that this method of estimating the effects of treatment on response is reasonable, given the lack of evidence for comparators based on the same definition of treatment response. We do have some questions about the method of implementation in the company model:

- The method relies on a small IPD dataset for one treatment arm. This may bias results if the sample is not representative of UK patients with EDS due to narcolepsy. The method also assumes that the distributions of ESS change are similar for the different treatments, which may not be accurate if the mechanisms of action for the treatments differ substantially.
- The main deterministic results of the model should be based on direct estimates from the original IPD dataset, not from a mean of bootstrapped samples.
- It is appropriate to use non-parametric bootstrapping of the IPD dataset in the probabilistic sensitivity analysis (PSA), as this takes account of individual differences in response without assumptions over the form of the distribution.

However, we think that the way in which bootstrapping was applied in the company's PSA will have underestimated uncertainty.

Treatment discontinuation

The model does not include an explicit reassessment of response (a 'stopping rule'), but it does assume that a proportion of patients will stop treatment in the initiation phase and in ongoing maintenance treatment due to loss of response or adverse events. Ongoing rates of discontinuation due to loss of response and treatment related adverse events are based on data from the TONES 2 and TONES 5 trials:

- Discontinuation due to loss of response was estimated at 10.9% per year. It is not possible to validate this estimate, as we do not have access to the relevant information from the pivotal trials. Clinical advice suggests that the discontinuation rate due to loss of response is slightly lower in clinical practice.
- Discontinuation due to adverse events after titration were estimated at 4.4% per year. This is likely to be an overestimate as the solriamfetol arm in TONES 5 included the unlicensed 300 mg dose.

The model assumes that ESS returns to the mean baseline value immediately after treatment discontinuation. The company justifies this based on results from the two-week randomised-withdrawal phase of TONES 5, and the half-life for solriamfetol and the comparators. The company did not conduct any sensitivity analyses over more gradual waning of treatment effects after discontinuation.

Utilities

The company did not use EQ-5D-5L results from trial data to estimate utilities for the model. To justify this they suggest various reasons to explain why the TONES 2 trial did not detect a significant effect on EQ-5D index scores, including omission of dimensions relevant to daytime sleepiness from the instrument and adaptation of patients' lifestyle and expectations. We agree with these points, but note that the trial also failed to find a statistically significant effect on a range of other quality of life measures. We also observe that the trial is unlikely to have had sufficient power to detect changes in EQ-5D utility scores; and that the 12-week study period would have been too short to effect changes to ingrained behaviour or expectations.

In this situation, it is reasonable to consider a mapping approach, although this does introduce additional uncertainty. As the model structure is based on change in ESS as the measure of treatment effect, an analysis that links ESS with utility is required. The company note the analysis conducted for NICE TA139 on continuous positive airway pressure for obstructive sleep apnoea (OSA). This used an algorithm (the 'McDaid formula'), which predicts that a one-unit increase in ESS scores is associated with a fall of 0.01 in utility.

The company used a similar approach to estimate utility as a function of ESS in people with EDS due to narcolepsy. This used individual-level data from the National Health and Wellness Survey (NHWS) 2016. The sample includes people in five EU countries, including the UK, who reported experience of OSA and/or narcolepsy in the past 12 months: 2,348 people [redacted].

The dataset is large, but only has a small proportion of people reporting narcolepsy. The sample may be subject to recruitment bias due to the use of an online sample and self-reporting of diagnosis. So it is not clear whether the estimation sample is sufficiently similar to the target sample of people with narcolepsy in the UK. We consider that the process of data analysis and model fitting was good, following the process recommended by the NICE Decision Support Unit (DSU). There is some uncertainty over the valuation of the EQ-5D-5L data. It is stated that the 'crosswalk' method is used (as recommended by NICE), but not whether the UK value set was used for all participants.

The final model includes a 'break-point', with greater change in utility per unit change in ESS for ESS scores above 11 (coefficient [redacted]) than for ESS scores less than or equal to 11 (coefficient [redacted]). The equation adjusts for a wide range of variables, but most are not available in the TONES 2 data, and so in practice the model estimates utility as a function of reported disorder (OSA alone, OSA with narcolepsy, narcolepsy alone), age, sex and treatment-related ESS score, with a fixed term reflecting a background level of utility.

The utilities in the company's base case are estimated by applying the NHWS formula to ESS changes in TONES 2. These values may lack face validity as they are much lower than UK general population norms, EQ-5D index scores from TONES 2 and TONES 5 and values for narcolepsy reported in the literature. However, this does not matter if the ESS-utility relationship is accurate, because given the model structure and assumptions, the ICER is driven by between-treatment differences in utility, not by absolute utility values.

On balance, we agree with the company's use of the NHWS mapping algorithm in their base case, with the McDaid formula in a scenario.

Resource use

Drug acquisition cost is the only cost category included in the company's economic analysis. Assessment of treatment response is assumed to take place at week 8 for all treatments, and therefore, drug acquisition in the treatment initiation phase is costed up to week 8.

Mean and median healthcare costs over the 1-year period were planned outcomes in TONES 5 (TONES 5 CSR page 6). As reported in the TONES 5 CSR, healthcare resource use, including doctor appointments and hospitalisation due to serious AEs, showed a possible trend towards [redacted] utilisation in patients treated with solriamfetol 150 mg compared to solriamfetol 75 mg dose. However, these costs are not considered in the company's analysis.

Based on clinical advice, the modelled equal shares for sodium oxybate 4.5 g, 6 g and 9 g doses; and the assumption that one third of patients receive 18 mg/day and two thirds are given 36 mg/day of pitolisant in clinical practice are reasonable.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions are shown below:

- Patient baseline demographic and disease characteristics (we use the characteristics of the whole eligible population recruited to the pivotal trial and received treatment)
- Definition of treatment response (ESS≥2)
- Hospitalisation due to SAEs (included)
- The cost of medical appointments (included)
- Solriamfetol 75 mg and 150 mg market share (10%/90%)

Further details are provided in Table 40.

Table 1 ICER resulting from ERG's preferred assumptions

	Treatment	Total Costs	Total QALYs	Pairwise: Sol vs comparator CER	ICER (QALY)	ICER Ranking
ERG base case	Solfiamfetol combined	£23,086	13.547	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£253,654	Dominated	
	Sodium oxybate combined	£42,309	13.483	-£299,829	Dominated	

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG's scenario analyses and subgroup analysis are shown below:

- Population characteristics: 50% female
- Model time horizon: 1 year, 5 years, 15 years and 20 years
- Clinical effectiveness: time point (12 weeks) and time of treatment response at 2 weeks
- No treatment discontinuation multipliers due to loss of response and TEAEs for comparators
- Definition of response: reduction in ESS≥4 points
- The cost of medical appointments applied every 6 weeks for non-responders
- Market share - Solriamfetol 75 mg at 20%
- Market share - Sodium oxybate 4.5 mg 10% and Sodium oxybate 6 mg 10%
- Prior modafinil
- ERG base case including methylphenidate (40 mg) and dexamfetamine (40 mg) as comparators

Results and details of these analysis are provided in section 6.2.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Jazz Pharmaceuticals on the clinical effectiveness and cost effectiveness of solriamfetol for treating excessive daytime sleepiness caused by narcolepsy. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 3rd February 2020. A response from the company via NICE was received by the ERG on 17th February 2020 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on narcolepsy

CS Section B.1.3 provides an overview of the condition narcolepsy, describing patient symptoms (excessive daytime sleepiness (EDS) being the primary symptom), patient burden, epidemiology and health care burden. Expert clinical advice to the ERG, where given, generally concurs with the information on narcolepsy presented in the CS. In relation to patient subgroups, the CS distinguishes patients according to the presence or absence of concomitant cataplexy. Cataplexy is a sudden loss in muscle tone triggered by strong emotions ranging from mild weakening of the facial muscles to total collapse on the floor.[1] One of our clinical advisors commented that diagnostic criteria for narcolepsy were updated in 2014 and patients are currently distinguished as having type 1 or type 2 narcolepsy.[2] Type 1 patients (previously termed 'narcolepsy with cataplexy') have evidence of either a low hypocretin level on lumbar puncture test or presence of cataplexy in addition to objective evidence of sleep-onset rapid eye movement (REM) from a specialised nap test known as the Multiple Sleep Latency Test (MSLT). Type 2 patients (previously termed 'narcolepsy without cataplexy') usually have normal hypocretin levels but experience EDS without cataplexy. The CS reports that 70% of narcolepsy patients have cataplexy, whereas the estimates of narcolepsy patients with type 1 narcolepsy from our clinical expert advisors span a range of 50%-87.5%.

2.2.2 Background information on solriamfetol

Solriamfetol is licensed for the indication of improving wakefulness and reducing EDS in adult patients with narcolepsy (with or without cataplexy). It is not licensed for use in children. The recommended starting dose in patients with narcolepsy is 75 mg once daily, upon awakening. The dose can be titrated to a higher level by doubling the dose at an interval of at least 3 days, with a recommended maximum daily dose of 150 mg once daily. In patients with more severe levels of sleepiness, a starting dose of 150 mg may be considered. Although the CS presents clinical trial evidence in respect of a 300 mg daily dose of solriamfetol, this dose is not licensed.

Solriamfetol is also indicated to improve wakefulness and reduce 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). A lower starting dose (37.5 mg daily) is recommended for this indication.

Solriamfetol is a centrally-acting sympathomimetic psychostimulant. Its mechanism of action in treating the symptoms of narcolepsy and OSA is not fully known, but it is thought that its effect may be mediated through its pharmacological action as a dopamine and norepinephrine reuptake inhibitor (DNRI).[3]

2.2.3 The position of solriamfetol in the treatment pathway

The CS description of current narcolepsy health service provision and the clinical care pathway is significantly informed by interviews conducted by the company in 2019 with UK healthcare practitioners (HCP) (n=9) and key opinion leaders in the management of narcolepsy (KOL) (n=7). (NB. the information derived from these interviews are used to inform some of the assumptions in the company's economic model, as we describe in section 4 of this report).

Recommendations from European narcolepsy treatment guidelines are summarised, but are said to not be widely recognised in UK practice. Notably, there is an absence of available UK narcolepsy management guidelines. A discussion of the limitations of currently used narcolepsy therapies is provided, and the case for solriamfetol in meeting unmet need is given, again, informed by key opinion leader information.

In describing the current treatment pathway, the CS suggests, based on the interviews with KOLs, that the only treatment widely available for treating narcolepsy in the UK is modafinil, and that this is the established first line treatment. Expert advice to the ERG concurs. The CS estimates that 20%-66% of patients may not respond to first line modafinil. Our expert advisors estimated a similar range (10%-55%) but also noted that if a partial response is achieved, some clinicians may add another treatment, while others may switch to a different treatment. Some patients (number not specified in the CS) cannot receive modafinil due to contraindications, drug interactions and cautions. The ERG's clinical experts advised this may apply to 10%-20% of patients. The CS states that there is wide variation in practice for treatments given at second line for patients failing to respond to modafinil (NB. These would effectively be first line treatment for patients contraindicated to modafinil). Second line treatments may include any of the following drugs: methylphenidate, dexamfetamine, sodium oxybate, or pitolisant [NB. methylphenidate, dexamfetamine are not licenced for the treatment of narcolepsy but dosing information is included for narcolepsy in the British National Formulary (BNF)]. Our clinical experts agreed with the company's estimated (declining) narcolepsy market share of 17.4% and 2.7% for dexamfetamine and methylphenidate, respectively. Expert clinical advice to the ERG also confirmed that prescribing practice may vary between clinicians according to preference and local prescribing guidance.

The ERG notes that modafinil, pitolisant and sodium oxybate have not been appraised by NICE for the treatment of narcolepsy. The current appraisal of solriamfetol will therefore be the first NICE appraisal of a treatment for narcolepsy. NICE has previously appraised treatments for obstructive sleep apnoea - NICE TA139 "Continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnoea/hypopnoea syndrome (OSAHS)", published in 2008.[4] Some of the assumptions used to inform the company's economic model in this current appraisal are informed by TA139, on the justification that EDS is a key symptom common to OSA and narcolepsy, and thus are applicable in the current appraisal. The ERG considers this reasonable, though notes that TA139 is now over 10 years old and more recent data may be more appropriate.

ERG conclusion

The description given in the CS of the characteristics of narcolepsy and its management is clear and detailed. To inform their submission the company conducted interviews with health professionals and opinion leaders in the management of narcolepsy. This is appropriate given the lack of UK narcolepsy clinical guidelines. Expert clinical advice to the ERG, where given, generally concurs with the information presented in the CS.

2.3 Critique of company's definition of decision problem

Table 2 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the ERG's comments on this.

Table 2 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with excessive waketime sleepiness caused by narcolepsy.	The population is more appropriately described as: Adults with narcolepsy (with or without cataplexy) who suffer from EDS and have failed to respond to, are intolerant to, or in whom modafinil is contraindicated.	The company problem submission more accurately reflects the clinical data, population studied, licensed indication and likely place in UK clinical practice, based on advice from KOL Clinical Practice Interviews with consultants who treat patients with narcolepsy.	The company have restricted the population in their decision problem to adult narcolepsy patients with EDS who have failed, or who are intolerant to modafinil, or for whom modafinil is contraindicated. Clinical advice to the ERG was that modafinil was likely to remain the first-line treatment option. The positioning of solriamfetol for use as a second-line treatment option or when modafinil is contraindicated appeared appropriate. Only adult patients are covered by the licenced indications for solriamfetol.
Intervention	Solriamfetol	Solriamfetol	Solriamfetol	Appropriate

Comparator(s)	• Modafinil • Dexamfetamine • Methylphenidate (unlicensed in narcolepsy) • Sodium oxybate • Pitolisant	• Dexamfetamine • Methylphenidate (unlicensed in narcolepsy) • Sodium oxybate • Pitolisant	• There are no UK national guidelines on the management of narcolepsy but based on evidence from the Sleep Service Analysis and KOL Clinical Practice interviews, modafinil is the only treatment with an established place in clinical practice (first-line). Beyond first-line modafinil, there is substantial variation in local practice, depending on clinical opinion, preference, and local funding and/or guidelines. • Jazz requests that solriamfetol should be considered as a subsequent treatment option for patients in whom modafinil has failed, is not tolerated or is contraindicated. • As such comparison of solriamfetol with modafinil is not appropriate. • As highlighted in the NICE scope for this appraisal, methylphenidate does not hold a license specifically in patients with narcolepsy; it is only licensed in patients with ADHD.	The comparators are appropriate for the company's decision problem population (i.e. it is appropriate to exclude modafinil as a comparator because the company propose that solriamfetol is used as a second-line treatment option after modafinil or when modafinil is contraindicated).

			• Solriamfetol is the first treatment specifically for EDS in narcolepsy that has been assessed by NICE. None of the treatments identified in the NICE scope or company submission have been assessed by NICE.	
Outcomes	• Excessive waketime sleepiness • Adverse effects of treatment • Length of life • Health-related quality of life	EDS Adverse effects of treatment. Health-related quality of life	• The term EDS more appropriately describes the symptoms of sleepiness in patients with narcolepsy, and this is more reflective of the terminology used in clinical practice, than excessive waketime sleepiness. • As no effects of solriamfetol on mortality are anticipated, the submission does not model treatment related mortality but does model length of life using national life tables and adjusting for narcolepsy.	Appropriate

Source: CS Table 1, CS B.3.2

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company performed a systematic literature review to identify studies that would permit an indirect comparison between solriamfetol and relevant comparators in the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy.

Full details of the company's methods for the review are presented in Appendix D of the CS.

The review comprised:

- a search for all interventions of interest, limited to RCTs only
- an additional search to identify all published studies (of any study design) describing the use of stimulant drugs in narcolepsy (e.g. dexamphetamine or methyphenidate), as no RCTs had been found for this group of drugs.

The ERG's critique of the methods used in the CS is shown in Table 3.

Table 3 ERG appraisal of systematic review methods

Systematic review components and processes	ERG response (Yes, No, Unclear)	ERG Comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	PICOD framework described in CS Appendix D.1.3.1 Table 1 for RCT search and CS Appendix D.1.3.2 Table 2 for stimulants search.
Were appropriate sources of literature searched?	Yes	Sources include Medline, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, relevant clinical trial registries and conference abstracts.
What time period did the searches span and was this appropriate?	Yes	Searches are sufficiently recent (RCT search conducted on11th and stimulant studies search 24th October 2019). No restriction on time, except for exclusion of conference abstracts prior to 2016. The ERG has not conducted any updated searches.
Were appropriate search terms used and combined correctly?	Yes	The search terms are appropriate and have been combined correctly (CS Appendices D.1.1.1, D.1.1.2 and D.1.2.1).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Inclusion and exclusion criteria are specified for the RCT search in CS Appendix D.1.3.1 Table 1 and for the stimulants search in CS Appendix D.1.3.2 Table 2. Inclusion criteria are wider than required for the company decision problem but are considered appropriate.
Were study selection criteria applied by two or	Yes	Two independent reviewers applied the study selection criteria for screening of titles and abstracts

Systematic review components and processes	ERG response (Yes, No, Unclear)	ERG Comments
more reviewers independently?		and review of shortlisted full texts (CS Appendices D.1.3.1 and D.1.3.2).
Was data extraction performed by two or more reviewers independently?	Yes	Two independent reviewers performed data extraction for the studies identified in the RCT search (CS Appendix D.1.3.1). The project manager performed independent quality control on 10% of all articles extracted. No studies were identified from the stimulants search that could be included in the indirect treatment comparison. Data extraction variables are not provided in detail but included characteristics of studies, interventions and patients as well as outcome data.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The CRD assessment tool[a] was applied to all eligible RCTs identified from the search. These assessments are tabulated in CS Appendices D.3 Table 84 and D.1.5.4 Tables 21-25. Two additional questions were added to the CRD tool regarding the use of concomitant therapies and whether the treatment dose reflected recommended clinical practice. Eligible non-RCTs were assessed using a 20 question checklist for case series studies from the Institute of Health Economics, Alberta, Canada (CS Appendix D.3, Table 85).[5] The ERG's review of the company's risk of bias assessment is summarised in section 3.2.2 of this report.
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	Unclear	The CS does not provide details of who performed the risk of bias assessment.
Is sufficient detail on the individual studies presented?	Yes	Considerable detail is provided for the individual studies on solriamfetol (CS Section B.2.3 and for comparators include in the indirect treatment comparison (CS Appendix D.1.4 and D.1.5.1). The company provided additional information in response to clarification questions A23, A29 and A31.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	Indirect treatment comparisons by network meta-analysis was undertaken using appropriate methods. For a full critique see Section 3.3 and Section 3.4 of this ERG report.

[a] https://www.york.ac.uk/crd/guidance/

ERG conclusion

The ERG considers the company's methods for the systematic review of clinical effectiveness to be appropriate. All relevant studies are likely to have been identified.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The CS review of clinical effectiveness (section B.2 of the CS) includes evidence from three trials of solriamfetol (TONES 2, TONES 1 and TONES 5) in the treatment of EDS associated with narcolepsy. The company or, for TONES 1, the company from whom Jazz Pharmaceuticals acquired a licence to develop and commercialize solriamfetol, sponsored these trials. The ERG considers that all relevant studies for solriamfetol have been included. The exclusion of earlier phase studies and studies of solriamfetol in other indications (such as OSA and depression) is considered appropriate. Data from an additional trial assessing the effect of solriamfetol on driving performance (NCT02806908) are not available at the time of this submission.

Trial characteristics

Table 4 summarises the TONES trials' study characteristics. The primary efficacy outcomes were defined by the change from baseline in one or more sleepiness-related measures at various time points. The ERG's review of the efficacy, safety and HRQoL outcomes are fully elaborated in section 3.2.3 of this ERG report. The CS reports on final data cuts for all three studies.

The pivotal phase III RCT TONES 2 was a four-arm trial: three solriamfetol arms (75 mg, 150 mg and 300 mg doses) and a placebo arm. The phase IIb RCT was a two-arm trial: Solriamfetol 150 mg (weeks 1-4) increasing to 300 mg once daily (weeks 5-12). TONES 5 was an open-label study with a combined solriamfetol dose arm (75-300 mg) that also included a 2-week randomised withdrawal component. The objective of the open-label study was to evaluate the safety and tolerability of solriamfetol for up to 52 weeks. The objective of the randomised-withdrawal phase was to evaluate the maintenance of efficacy of solriamfetol by randomising patients to continue on their stable dose of solriamfetol or switch to placebo following a minimum of 26 weeks open-label treatment with solriamfetol.

All three studies therefore included use of the 300 mg unlicensed dose of solriamfetol, however, data are only presented in the CS for this dose as part of the combined dose arm in the TONES 5 long term study. Data from TONES 1 is considered up to week 4 only as the 300 mg dose was used beyond this time point.

The long-term TONES 5 study enrolled patients who had completed solriamfetol trials in narcolepsy (including TONES 1 and TONES 2) as well as patients who had completed solriamfetol trials in OSA. The duration of the open label phase was either 40 weeks, if the patient enrolled directly from a previous trial without a break (Group A), or 52 weeks if they had enrolled after historical participation in a previous study after which they may have had a break (Group B). Details of the TONES 5 study populations are available in Appendix 1 of this report.

Table 4 Characteristics of the three TONES trials

Characteristic	TONES 2	TONES 1	TONES 5	
Study design	Phase III multicentre, randomised, double-blind, placebo-controlled, four-arm parallel-group	Phase IIb multicentre, randomised, double-blind, placebo-controlled, two-arm parallel-group	Phase III open-label study including a 2-week randomised withdrawal phase for a subgroup of the enrolled population after completion of ≥6 months of solriamfetol treatment	
Population	Adult patients with narcolepsy[a] who had EDS (ESS score ≥10) and difficulty maintaining wakefulness (mean sleep latency <25 minutes)[c]	Adult patients with narcolepsy[b] who had EDS (ESS score ≥10) and difficulty maintaining wakefulness (mean sleep latency ≤10 minutes)[c]	Adult patients who had previously completed solriamfetol clinical trials in narcolepsy or OSA indications (including TONES 1 and TONES 2).	
Intervention	Solriamfetol 75 mg, 150 mg or 300 mg once daily for 12 weeks	Solriamfetol 150 mg (weeks 1-4) increasing to 300 mg once daily (weeks 5-12)	Solriamfetol (combined dose arm: 75, 150 or 300 mg once daily); patients were up-titrated every three days starting at 75 mg to a maximum tolerated dose (300 mg unlicensed) for 40-52 weeks	
Comparator	Placebo, once daily	Placebo, once daily	Open-label phase (40-52 weeks)	2-week withdrawal phase
			None	Placebo, once daily
No. randomised	239	93	643 treated (226 with narcolepsy)	282 (79 with narcolepsy)

Characteristic	TONES 2	TONES 1	TONES 5	
Randomisation ratio	1:1:1:1	1:1	Not applicable	1:1
No. completed	195	74[d]	458 (150 with narcolepsy)	278 (78 with narcolepsy)
No. of centres	59 (US, Canada, Finland, France, Germany & Italy)	28 (US)	79 (North America & Europe)	
No. of UK centres	Nil	Nil	Nil	
Primary Outcome(s)	Change from baseline ESS and MWT at week 12	Change from baseline MWT at week 12 (unlicensed 300 mg dose so not considered in CS); % of patients rated as improved by CGI-c at last the assessment	Not applicable	Change in ESS from beginning to end of 2-week withdrawal phase
Sub-groups	Cataplexy status, region and country	Cataplexy status	Indication (narcolepsy or OSA), cataplexy status and region	

Source: This table was compiled by the ERG from information presented in CS Sections B.2.3.1.1 and Appendix D.2
Abbreviations: EDS Excessive daytime sleepiness; ESS Epworth sleepiness scale; OSA obstructive sleep apnoea; CGI-c Clinical Global Impression of Change
[a] diagnosed according to the ICSD-3 or DSM, 5th edition criteria; [b] diagnosed according to the ICSD-2 criteria; [c] based on the mean of the first four trials of a 40-minute Maintenance of Wakefulness Test [MWT]; [d] the ERG notes an error in participant flow diagram in CS Appendix D.2.2 whereby numbers of withdrawals are inversed for the two trial arms. Additionally it is unclear whether patients without a post-baseline efficacy measurement have been considered as completing the study.

Baseline Characteristics

Patients' baseline characteristics (CS Section B.2.3.2 Tables 7, 9 and 10) in the three TONES trials were similar and the ERG's review of these is summarised in Table 5. A summary of baseline characteristics for TONES 1 and TONES 2 is also available in Appendix 2 of this ERG report. Overall, the trial populations appear to be aligned with the company decision problem in that they represent adult patients with narcolepsy in whom earlier therapy may have been unsuitable or inadequate. It is unclear to what extent the trial populations are fully representative of the wider population with narcolepsy in the UK as data on patient demographics in narcolepsy are limited and all three trials were predominantly conducted in the US and Canada.

Table 5 ERG Review of Baseline Characteristics of Participants in TONES trials

Baseline Characteristic	ERG Comment
Ethnicity	Most patients were white ([redacted]) which is consistent with the UK population.
Sex	A higher proportion of patients were female ([redacted]%) which may mean that men with narcolepsy were not fully represented
Age	The mean age of trial participants ([redacted] years across all trial arms) appeared to be lower than the adult UK narcolepsy population which has been previously reported as around 54-56 years,[6,7] although the ERG acknowledges that the latter estimates may be out of date.
BMI	Mean BMI across the whole trial populations of the three studies ranged from [redacted] which is in line with that of adults in the UK.[8] Higher BMI has been observed in patients with narcolepsy.[9]
Severity of illness	Most patients (96%) were at least moderately ill (according to their baseline CGI-s score in TONES 2 and TONES 5) with mean baseline ESS scores in the range of [redacted].
Prior use of narcolepsy medication	In TONES 2 [redacted] had used previous narcolepsy medications with almost half of patients reporting prior use of modafinil, which is regarded by clinical experts as the first-line drug treatment option. The company's response to clarification question A1 reports that no data were collected on whether modafinil had been used first-line or reasons why some patients did not receive modafinil in the TONES 2 RCT.
Cataplexy status	Around [redacted] of the trial patients (TONES 2) had cataplexy which is lower than the estimated prevalence (70%) in the wider narcolepsy population reported in the CS Section B.1.3. The company suggest (response to clarification question A3) that this may be partly due to sampling error (due to small sample sizes) and partly because patients with cataplexy may not have wished to stop their anti-cataplexy medication which was a requirement for entering the trial.
HRQoL measures (described in section 3.2.3 of this ERG report)	In TONES 2, baseline EQ-5D-5L scores indicated that [redacted]% of patients had utility scores=1 suggesting no disutility due to narcolepsy. It is unclear whether this is due to lack of sensitivity of this generic measure in narcolepsy patients or due to the trial population being less affected by narcolepsy than would be expected from a population where most patients had at least moderate illness. However, baseline FOSQ-10 scores, a measure that is more specific to sleep-related issues, were lower (scores of 11.4 to 12.2 points) than normal values (18 points).

Source: Compiled by ERG using information presented in CS Sections B.2.3.2 and B.2.6.1.8

Eligibility criteria for the TONES studies (CS Appendix L.1.1 Tables 129 to 131) appeared to be reasonably inclusive in terms of patient demographics but it is possible that trial populations may be less representative of patients with certain comorbidities, e.g. severe cardiovascular disease as these patients were excluded from the trials. The ERG also notes that the protocol-driven dose titration used in the TONES trials may not reflect the dose regimen in clinical practice.

Baseline characteristics of the subset of TONES 5 patients who took part in the randomised withdrawal phase are described in the CS (Section B.2.3.2.3.2) as similar to the patients in the open-label period but no further details are given.

With respect to internal validity, baseline characteristics were broadly similar between trial arms with respect to age, race, BMI, ESS score and disease severity. Some differences were observed in sex distribution between trial arms in TONES 2 ([redacted]% male in placebo group, [redacted]% in solriamfetol 150 mg group) and for prior modafinil use ([redacted] in placebo group and [redacted] in solriamfetol 150 mg group). The significance of these imbalances is unknown, as no evidence has been presented in the CS or from clinical experts to suggest that sex or prior use of modafinil would be a significant predictor of response to solriamfetol.

ERG conclusion on included studies

Inclusion of the TONES 2 RCT as the main source of evidence of clinical effectiveness is considered appropriate. TONES 1 provides supporting information on efficacy and safety but this is of limited utility as this trial only provides relevant data for the first 4 weeks of treatment. TONES 5 provides longer-term data on efficacy and safety of solriamfetol and the effects of withdrawal of solriamfetol. It is unclear how representative the trial populations are to the target population of adult patients with narcolepsy in England.

3.2.2 Risk of bias assessment

TONES 2 AND TONES 1 trials

The company conducted quality assessment of TONES 2 and TONES 1 trials using NICE recommended criteria (CS section B.2.5 and Appendix D.3). The ERG independently conducted quality assessment using these criteria (Table 6). The company and ERG were in general agreement that the trials are of good methodological quality and low risk of bias.

The following minor issues were identified:

- The company and the ERG both noted some differences between the respective trial's arms at baseline (placebo versus solriamfetol dose arms, and between solriamfetol dose arms) in variables such as sex, race, and CGI-s score. These differences were more pronounced in the TONES 2 trial. It is not known whether any of these variables are prognostic or effect modifiers for narcolepsy treatment. The

ERG's view therefore is that it's unclear what, if any, bias this may have on the trial results.

- Unexpected imbalances between the arms of the respective trials in the proportion of patients dropping out early were not identified, with the exception of TONES 2 in which the highest percentage of overall drop out was in the 300 mg solriamfetol dose arm (27%). The CS suggests the higher rate seen in the 300 mg dose group was because the incidence of AEs was generally dose-dependent (withdrawals due to AEs were highest in this arm). As noted earlier, the 300 mg dose group is not relevant to this appraisal, therefore examination of the percentage of patient withdrawals in just the placebo and 75 mg and 150 mg arms shows no consistent pattern (10%, 17%, 7%). Furthermore, in each trial arm there was there no reason for withdrawal that was more common than other reasons, with the exception of the 75 mg arm in which the most common reason for withdrawal was lack of efficacy (n=4 patients), which was twice that of withdrawal due to AEs (n=2 patients). The ERG concludes there is no consistent reason for imbalance in patient drop out across the trial arms. It is unlikely that the imbalance would cause significant risk of bias.
- The modified intention-to-treat (mITT) analysis used in TONES 2 comprised all patients who received ≥1 dose of study drug and had a baseline and ≥1 post-baseline evaluation of ESS or MWT (NB. TONES 1 used an ITT analysis, defined similarly to the mITT analysis in TONES 2 but there were no patients who lacked a baseline evaluation). In both trials the proportion of randomised patients who were excluded from the mITT/ITT population was around 3% and thus any bias arising from their exclusion is likely to be low (see section 3.2.4 for our critique of the trial statistical methods).

Table 6 Quality assessment results for parallel group RCTs (TONES 2 and TONES 1)

Trial ID	TONES 2		TONES 1	
	Company	ERG	Company	ERG
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No

Trial ID	TONES 2		TONES 1	
	Company	ERG	Company	ERG
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes
Are conflicts of interest reported?	Yes	Yes	Yes	Yes
Were concomitant therapies aside from the trial drug(s) allowed?	Yes	Yes	Yes	Yes
Does treatment administration reflect recommended clinical practice (i.e., initial dose and titration)?	Yes	Yes	No	No

Source: Adapted from CS Table 14

TONES 5 study

As described earlier, TONES 5 was a long-term, open-label extension safety and maintenance of efficacy study, which included patients treated with solriamfetol in the TONES 1 and 2 trials (as well as trials of solriamfetol in the treatment of OSA). There was no comparator to solriamfetol in this study, except during a two-week randomised placebo-controlled withdrawal phase part way through.

The company assessed the quality of this study using the 20-item Quality Appraisal Checklist for Case Series Studies instrument from the Institute of Health Economics, Canada (CS section D.3). The checklist includes criteria related to the study design and objectives, the characteristics of the study population, the description of the intervention(s), the definition and measurement of outcomes, the statistical analyses used, and the presentation and interpretation of results. Many of the criteria cover the quality of the conduct and reporting of the study, with some covering its risk of bias (e.g. blinding of study personnel during the randomised withdrawal phase).

Accordingly, the ERG independently assessed the quality of this study using the same instrument and agreed with the company's judgements on each criterion. The CS does not provide an overall judgement on the methodological quality of the study. The ERG's judgement is that, based on the criteria, the study is well conducted and reported, with the biggest limitation (and therefore potential for bias) being the lack of a comparator arm (except during the randomised withdrawal phase).

3.2.3 Outcomes assessment

In this section we describe the key efficacy, safety and HRQoL outcomes, focusing particularly on the pivotal TONES 2 RCT and the outcomes which inform the economic model. Full details on all trial endpoints for the three TONES trials are described in CS Section B.2.3.1.3 Table 5.

3.2.3.1 Main efficacy outcomes

The main efficacy outcome of interest described in the NICE scope is excessive waketime sleepiness. The company suggests that the term excessive daytime sleepiness (EDS) better describes the language used in clinical practice. Two different types of measure have been used to assess EDS in the TONES trials: the subjective, Epworth Sleepiness Scale (ESS) and the objective, Maintenance of Wakefulness Test (MWT). The change from baseline in ESS at week 8 is used as the measure of treatment response in the company's base case economic model. Table 7 summarises the outcomes measured in the TONES 2 trial.

Table 7 Outcome measures: TONES 2

Outcome type	**Outcome measures** (CS Table 5)	**Outcome definitions** (CS Table 6)	**ERG comments**
Epworth sleepiness scale (ESS):			
Co-primary efficacy	Change from baseline to week 12	Patients were asked to complete the ESS with regard to the level of sleepiness they experienced over the [redacted], using the questionnaire validated for this duration. Patients respond to eight questions asking how likely they would be to doze off or fall asleep in eight different situations. Total scores range from 0–24, with higher scores	Subjective, validated patient self-assessment tool[10] • ≥3-point reduction used to define response for the company's base case economic model (CS Section B.3.3.1) References used to support definition of response as ≥3-point reduction based on data on patients with narcolepsy and OSA from the TONES studies themselves. [11-13] Clinical
Secondary efficacy	Change from baseline to weeks 1, 4 and 8		
Post-hoc analyses	Percentage of patients with a normal ESS score (ESS ≤10) at week 12		

Outcome type	Outcome measures (CS Table 5)	Outcome definitions (CS Table 6)	ERG comments
		representing more severe sleepiness, therefore a reduction from baseline score represents an improvement. Scores ≤10 are considered within the normal range. The company have proposed that a minimum clinically important difference is estimated to be -2 to -3 points.	experts generally agreed with this assumption.
Maintenance of wakefulness test (MWT), change in mean sleep latency time (minutes), from baseline to endpoint:			
Co-primary efficacy	Change from baseline to week 12 determined from first four trials of 40-minute MWT (MWT40)	MWT evaluations were performed subsequent to an overnight stay at the study site for nocturnal polysomnography (PSG) according to a standard protocol. The MWT provides a validated objective assessment of the ability of a participant to remain awake. Measurements of sleep latency using the MWT40 range from 0 to 40 minutes. A positive change from baseline represents an improvement.	• Clinical experts report this is not used extensively to monitor treatment response in practice. References to validation studies have been provided. [14-16] • The ERG notes that a minimally detectable change relative to placebo was considered to be 6 minutes as per the sample size calculation provided in CS Table 13. It is unclear whether this is likely to be a clinically important change.
Secondary efficacy	MWT40 change from baseline to week 4		
	Time course of efficacy on MWT: Change in sleep latency time (minutes), at weeks 4 and 12, on each of a series of five 40minute MWT trials.		
Patient Global Impression of change (PGI-c) score:			

Outcome type	Outcome measures (CS Table 5)	Outcome definitions (CS Table 6)	ERG comments
Key secondary efficacy	Percentage of patients who reported improvement at week 12	Patients rate the change in their condition on a seven point scoring system: 1=very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; 7 = very much worse.	• The central point of the scale 4= no change. • This outcome has been dichotomised to 'improved' (score of 3 or less) or worsened' (score of 5 or more), which means it is not possible to know the degree to which participants considered they were improved or worsened (i.e. differences could all be minimal but this would not be captured).
Secondary efficacy	PGI-c: percentage of patients who reported improvement at weeks 1, 4 and 8		
Clinical Global Impression of change (CGI-c) score:			
Secondary efficacy	Percentage of patients reported as improved at weeks 1, 4, 8 and 12.	Investigators rate the change in the patient's condition from 1=very much improved to 7=very much worse as for the PGI-c.	• The central point of the scale 4= no change • As noted for the PGI-c this outcome has been dichotomised to 'improved' (score of 3 or less) or worsened' (score of 5 or more) which means it is not possible to know the degree to which investigators considered the participants were improved or worsened

Source: CS Table 5 and Table 6

TONES 1 RCT

In TONES 1 the primary co-efficacy outcomes were mean change from baseline in MWT40 and % of patients improved (assessed by CGI-c score) at week 12 (CS Table 5). This 12-week timepoint relates to the 300 mg solriamfetol dose, hence the relevant efficacy outcomes of interest for the 150 mg dose were the secondary efficacy outcomes:

- change from baseline in MWT40 and ESS at week 4.
- % of patients improved at week 4 as measured by PGI-c and CGI-c scores.

TONES 5 study

In TONES 5, ESS, PGI-c and CGI-c were measured at various time points (Table 8). For the patients who entered the randomised-withdrawal phase, the primary efficacy endpoint was change in ESS from the beginning to the end of the randomised-withdrawal period.

Table 8 Efficacy outcomes measured: TONES 5

TONES 5	
Open-label phase	**Two-week randomised-withdrawal phase**
Outcomes were reported separately for Group A and B[a]**.** **ESS** (Group A): Change over time from baseline in the parent study, and from last assessment in the parent study at weeks 2, 14, 27 and 40 **ESS** (Group B): Change over time from TONES 5 baseline at weeks 2, 14, 26, 39 and 52	**Primary efficacy endpoint** **ESS**: Change from the beginning to the end of the randomised-withdrawal period
Outcomes were reported separately for Group A and B. PGI-c: percentage of patients who reported improvement[b] from beginning treatment to each time point. CGI-c: percentage of patients reported as improved[b] from baseline to each time point.	**Secondary efficacy:** PGI-c: percentage of patients who reported worsening[c] at the end of the randomised withdrawal phase. CGI-c: percentage of patients reported as worse[c] at the end of the randomised withdrawal phase.

Source: Adapted from CS Table 5, Figure 7 and Figure 8
[a] Group A patients enrolled directly from a previous solriamfetol trial without a break; Group B patients enrolled after historical participation in a previous solriamfetol trial after which they may have had a break.
[b] minimally, much or very much improved or greater; [c] minimally, much or very much worse

3.2.3.2 Safety outcomes

Treatment-emergent adverse events (TEAEs), serious TEAEs (SAEs) and discontinuations were reported in all three TONES trials. Adverse events of special interest included insomnia, depression and suicidal ideation, cardiovascular events and changes in vital signs; and potential for abuse or withdrawal effects. Discontinuation rates due to TEAEs and discontinuation due to loss/lack of efficacy reported in TONES 2 and TONES 5 are used the company's economic model (CS Section B.3.3.4).

3.2.3.3 HRQoL outcomes

Change from baseline in a range of different HRQoL measures were used in TONES 2 (week 12) and TONES 5 (at same timepoints as efficacy outcomes) to measure the effect of the intervention on HRQoL. These measures included the Functional Outcomes of Sleep Questionnaire short version (FOSQ-10), Short-Form 36-Item Health Survey (version 2) (SF-36v2), European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP). Definitions for the HRQoL outcomes are provided in Appendix 3. However, none of the trial based HRQoL outcomes inform the base case economic model for reasons we discuss later in this report (Section 4.2.7).

3.2.3.4 Contribution of data from clinical effectiveness studies to economic model

TONES 2 was the key contributor, via the ESS outcomes, of clinical evidence for the base case economic model (Table 9). Data from TONES 5 were primarily used to support assumptions made in the economic model with respect to discontinuation rates due to adverse events or loss of efficacy over an extended time period (Section 4.2.6 of this report). The withdrawal phase of TONES 5 also provided evidence for the assumption that ESS scores would return to baseline levels after discontinuation. Data from TONES 1 were not used directly in the economic model but provided supporting evidence that ESS improvements can be seen from week 1.

Table 9 Contribution of outcome data to company's base case economic model

STUDY	OUTCOME	USE IN ECONOMIC MODEL	
TONES 2 RCT	Change in ESS at 8-weeks (secondary efficacy outcome)	CS Model base case	Week 8 IPD used for response estimates for solriamfetol
			ITC for mean change in ESS at 8 weeks used to generate relative treatment effects for comparators
	ESS (co-primary efficacy) – change from baseline to week 12	CS Model scenario	Week 12 IPD used for response estimate for solriamfetol
			ITC scenario using change in ESS at 12 weeks for solriamfetol (but only maximum of 8-week data for comparators) used to generate relative treatment effects.
	Discontinuation due to adverse events	CS Model base case	ITC of discontinuation due to TEAEs supports model assumption that rates of discontinuation during the initiation phase are equivalent for all treatments considered (B.3.3.4).

STUDY	OUTCOME	USE IN ECONOMIC MODEL	
	Discontinuation – loss of response	CS Model base case	Withdrawals due to loss of response in TONES 2 used in the calculation of discontinuation due to loss of response within the first year of the model.
TONES 5 OPEN LABEL	Discontinuation due to adverse events	CS Model base case	Open-label phase discontinuation due to TEAEs data is used to estimate what discontinuation in the maintenance treatment phase would be.
	Discontinuation – loss of response	CS Model base case	Withdrawals due to loss of response in TONES 5 open label phase used in the calculation of discontinuation due to loss of response within the first year of the model.

ERG Conclusion on Outcomes assessment

The efficacy outcome measures included in the CS comprise a mixture of (subjective) patient- and investigator-reported outcome instruments to assess sleepiness symptoms; disease-specific instruments to measure HRQoL and generic HRQoL instruments; and (objective) standard protocol-based polysomnographic monitoring of patients' ability to remain awake (sleep latency). These measures are reported to have been validated in the published literature, and some (such as the ESS) are commonly used in clinical practice. There is a lack of evidence to support the company's assumptions about definitions of improvement or worsening of symptoms, or minimal important clinical differences between treatment and placebo. However, expert clinical opinion supports some of these assumptions.

3.2.4 Approach to study statistics

In Table 10 below we summarise and critique the statistical methods used in the TONES studies. Further detail on these methods can be found in the CS (Section B.2.4.2).

In Table 10 below we summarise and critique the statistical methods used in the TONES studies. Further detail on these methods can be found in the CS (Section B.2.4.2).

Table 10 Summary of statistical methods used in the TONES studies

	ERG comments		
	TONES-2	**TONES-1**	**TONES-5**
Analysis populations	Three analysis sets are defined for each of the three TONES studies (CS Table 12): safety population, a modified intention-to-treat population (mITT) and a per-protocol population (PP).		

	The mITT was used for the analysis of primary endpoints (TONES 2) and for the analyses of the randomised-withdrawal phase (TONES-5). (NB. The TONES 1 trial is described as using an ITT rather than mITT analysis. The only difference between these two trials was that there were no patients with missing baseline assessments in TONES 1, whereas there were in TONES 2, which may explain the use of the term 'modified'). In response to clarification question A12 the company stated that only [redacted] out of 179 [redacted] across the placebo, 75 mg and 150 mg trial arms of TONES 2 were excluded from the mITT population because they did not take a dose of study drug or did not have at least baseline and one post-baseline MWT or ESS measure. The company highlight that use of a mITT population as the primary population for analysis was prespecified in the clinical trial protocol and was deemed appropriate by regulatory and ethics reviewers. The ERG considers that any potential bias from using a mITT analysis rather than an ITT analysis (i.e. based on all randomised patients) is likely to be small due to low percentage of patients excluded from mITT analysis set (around 3%).		
Sample size calculation	Reported in CS Table 13		
	It was estimated that 54 patients were needed per group, therefore it was planned to enrol approximately 60 per group. Appendix D.2.1 Figure 15 shows that slightly fewer than 60 patients were enrolled to each group and, after discontinuations, slightly fewer than 54 patients per group completed the study.	A minimum sample size of 41 patients per treatment group was considered sufficient, this was increased to 45 patients to allow for 10% missing data. Appendix D.2.2 Figure 16 shows that 74 patients completed the study (i.e. slightly fewer than 41 per treatment group).	For the 2-week randomised withdrawal phase approximately 150 patients per group was estimated to be sufficient. Although not explicitly stated in the CS the ERG assumes the groups are placebo and solriamfetol (regardless of dose received). Appendix D.2.3 Figure 17 shows [redacted]
Statistical approach for each outcome	Reported in CS Table 13		
	Fixed hierarchical testing was used to correct for multiplicity (i.e. potential to find significant results by chance when no underlying effect exists). Statistical significance was claimed only for outcomes above the break in the hierarchy with nominal p-values reported for differences below the hierarchical break. The ERG considers these measures to account for multiplicity appropriate due to the large number of outcomes and solriamfetol dose groups.	For the two co-primary endpoints an α-level was maintained at 0.05. No adjustments were made for multiplicity in testing other endpoints. The ERG notes the lower potential for multiplicity as there were fewer endpoints and only two trial arms.	A fixed hierarchical testing sequence was used to correct for multiplicity. Testing stopped when a significance level exceeded 0.05. At the end of the withdrawal phase patients randomised to solriamfetol were treated as single group regardless of the dose received (i.e. there were no multiplicity issues).
- Primary outcome(s)	Co-primary outcomes (ESS and MWT) analysed by MMRM model.	Co-primary outcomes (MWT and CGI-c) evaluated using two-sided t-tests.	Randomised withdrawal phase primary outcome: ESS evaluated using ANCOVA [redacted]
- Secondary and other endpoints	Chi-squared tests (PGI-c, CGI-c and EQ-5D-5L Dimensions)	Fisher's exact test (percentages of	Chi-squared tests (PGI-c, CGI-c)

	MMRM model similar to that used for the primary analyses (other ESS and MWT endpoints, FOSQ-10, SF36v2, EQ VAS, EQ-5D-5L Index, WPAI:SHP)	patients for CGI-c and PGI-c)	[redacted]
Handling of missing data	Primary endpoints – MMRM model & sensitivity analyses. PGI-c and CGI-c – missing data imputed using LOCF Other endpoints – MMRM model.	Primary endpoints – missing data imputed using LOCF Other endpoints presented as observed (i.e. no imputation of missing data)	[redacted]
Sensitivity analysis for statistical analyses	Four sensitivity analyses performed to assess the impact of missing data for co-primary endpoints: - [redacted] using single imputation (either LOCF or mean imputation) - [redacted] using multiple imputation (Markov change Monte Carlo with regression method and Pattern mixture model using dropout pattern imputation method).	Sensitivity analysis for one of the co-primary efficacy endpoints of MWT by ANCOVA was used to confirm treatment differences and evaluated potential site or treatment-by-site interactions.	[redacted]
Post-hoc analyses	Patients achieving normal ESS values and clinically meaningful change in ESS (mITT population using LOCF approach)	Effect size of mean MWT sleep latency change from baseline based on least squares mean divided by SD.	Patients achieving normal ESS values (LOCF approach)

ANCOVA = Analysis of covariance; LOCF = Last observation carried forward; MMRM = Mixed-effect model with repeated measures

ERG conclusion

The statistical methods used in the TONES studies are clearly reported and appropriate for the aims and designs of the studies. Patients were analysed according to mITT/ITT principles, with per protocol analyses used in secondary analyses; missing data were accounted for using single or multiple imputation approaches, with sensitivity analyses using alternative approaches; there was appropriate use of methods to minimise multiplicity (e.g. fixed hierarchical testing). The ERG did not identify any important limitations in the statistical analyses that would impact estimates of clinical effectiveness.

3.2.5 Efficacy results from the studies of the intervention of interest

3.2.5.1 Key efficacy results from pivotal phase III RCT: TONES 2 (CS Section B.2.6.1)

In this section we report on the co-primary outcomes, the company's designated key secondary outcome (PGI-c at week 12) and the secondary outcomes relating to ESS and MWT. We do not report on the PGI-c and CGI-c secondary outcomes which are summarised narratively by the company in CS Section B.2.6.1.7. The primary analysis was conducted for the mITT population: solriamfetol 75 mg (N=59), solriamfetol 150 mg (N=55) and placebo (N=58).

Co-primary efficacy outcomes:

Statistically significant improvements were reported for the co-primary efficacy outcomes (change in ESS and MWT) for solriamfetol 150 mg at week 12 (Table 11).

The mean improvement in ESS score from baseline to week 12 in both the solriamfetol 75 mg and 150 mg arms exceeded -3 and would therefore also be considered clinically significant. Effects were dose-dependent with a more modest effect observed for the 75 mg dose. Changes in MWT relative to placebo did not reach statistical significance for the 75 mg dose.

Table 11 Effects of solriamfetol on change in ESS and change in MWT compared to Placebo at Week 12

Co-primary outcome	Placebo (N=58)	Solriamfetol 75 mg (N=59)	Solriamfetol 150 mg (N=55)
Change in ESS from baseline			
LS mean (SE)	-1.6 (0.7)	-3.8 (0.7)	-5.4 (0.7)
Mean difference (95% CI, p-value) relative to placebo	-	-2.2 (-4.0 to -0.3, p=0.0211)	-3.8 (-5.6 to -2.0, p<0.0001)
Change in MWT from baseline			
LS mean (SE)	2.1 (1.3)	4.7 (1.3)	9.8 (1.3)
Mean difference (95% CI, p-value) relative to placebo (minutes)	-	2.6 (-1.0 to 6.3, p=0.1595)	7.7 (4.0 to 11.3, p<0.0001)

Source: CS Table 15

Secondary outcomes:

ESS and MWT:

- ESS and MWT improved at weeks 1, 4 and 8 relative to baseline in all three trial arms (CS Figures 4 & 5) with greatest improvements seen for the 150 mg solriamfetol dose. Compared to placebo, statistically significant differences in the change in ESS and MWT from baseline were consistently observed at all time points for the 150 mg dose only (CS Figures 4 and 5). Changes from baseline ESS at week 8 are shown in Table 11.

Table 11 Effects of solriamfetol on change in ESS compared to placebo at week 8

Secondary outcome	Placebo (N=58)	Solriamfetol 75 mg (N=59)	Solriamfetol 150 mg (N=55)
Change in ESS from baseline at 8 weeks			
LS mean (SE)	-2.1 [redacted]	-3.4 [redacted]	-5.2 [redacted]
Mean difference (95% CI, p-value) relative to placebo	[redacted]	[redacted]	[redacted]

Source: TONES 2 publication[17] supplemented with additional data from CSR Table 14.2.2.2.1

- A post hoc analysis showed that higher proportions of patients achieved a normal ESS score (≤10) at week 12 in the solriamfetol groups (30.5% for 75 mg and 40.0% for 150 mg) compared to placebo (15.5%) (CS Section B.2.6.1.5.1).
- Statistically significant changes in MWT from baseline were consistently greater for solriamfetol 150 mg compared to placebo in a series of five time points measured at 2 hour intervals throughout the day at week 12 (CS Figure 6) starting from within one hour of dosing. These effects were not sustained throughout the day for the 75 mg solriamfetol dose.

PGI-c score:

- For the company's designated key secondary outcome, higher proportions of patients reported improvement (categories of 'minimally', 'much' or 'very much' improved) in PGI-c score at week 12 in the solriamfetol groups (67.8% for 75 mg and 78.2% for 150 mg) compared to placebo (39.7%). Statistical significance was declared for the 150 mg dose vs placebo. The comparison of the 75 mg solriamfetol dose with placebo was below the hierarchical break in the fixed hierarchical testing approach used to account for multiplicity.

HRQoL outcomes:

Changes from baseline to week 12 in HRQoL scores obtained from the generic tools (SF-36v2, EQ-5D-5L Index and EQ-VAS) and the mean difference for solriamfetol 75 mg and 150 mg versus placebo at week 12 were reported. In addition, change in the total score using the disease-specific FOSQ-10 from baseline to week 12 and mean difference for the two solriamfetol doses versus placebo were also reported (CS Table 16).

[redacted] (Table 12).

The company note the lack of meaningful change in EQ-5D-5L scores in particular and suggest that the generic nature of this tool may not adequately capture changes in HRQoL in narcolepsy patients. The company provide justification of their use of an alternative HRQoL tool to calculate utilities in the economic model in CS Section B.3.4.

Table 12 TONES 2: HRQoL endpoints (mITT Population)

	Placebo N=58	**Solriamfetol 75 mg N=59**	**Solriamfetol 150 mg N=55**
Change in FOSQ-10 total score from baseline to week 12			
LS mean (SE)	1.6 [redacted]	2.4 [redacted]	2.6 [redacted]
LS mean difference vs. placebo		[redacted]	[redacted]
95% CI		[redacted]	[redacted]
p value		[redacted]	[redacted]
Change in SF-36v2 physical component summary score from baseline to week 12			
LS mean (SE)	1.1 [redacted]	2.5 [redacted]	2.65 [redacted]
LS mean difference vs. placebo		1.5	1.6
95% CI		−0.7 to 3.6	−0.5 to 3.2
p value (nominal)		0.1745	0.1430
Change in SF-36v2 mental component summary score from baseline to week 12			
LS mean (SE)	[redacted]	[redacted]	[redacted]
LS mean difference vs. placebo		[redacted]	[redacted]
95% CI		[redacted]	[redacted]
p value (nominal)		[redacted]	[redacted]

	Placebo N=58	Solriamfetol 75 mg N=59	Solriamfetol 150 mg N=55
Change in EQ-5D-5L Index from baseline to week 12 [a]			
LS mean (SE)	0.03 (0.014)	0.02 (0.014)	0.03 (0.014)
LS mean difference vs. placebo		-0.01	0.01
95% CI		-0.05 to 0.03	-0.03 to 0.04
p value		0.7267	0.7903
Change in EQ-VAS from baseline to week 12			
LS mean (SE)	3.1 (1.7)	2.7 (1.8)	1.9 (1.7)
LS mean difference vs. placebo		-0.4	-1.2
95% CI		-5.2 to 4.5	-6.0 to 3.7
p value		0.8807	0.6375

Source: Reproduced from CS Table 16 (footnotes edited)
Abbreviations: CI, confidence interval; CSR, clinical study report; EQ-5D-5L, 5-level EQ-5D version ; EQ-VAS, EuroQol Visual Analogue Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire short version; HRQoL, health-related quality of life; LS, least squares; SE, standard error; SF-36v2, Short-Form 36-item Health Survey version 2; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
[a] Crosswalk value sets for the EQ-5D-5L were used to derive the index scores. Values from UK were used if the country was not available; countries in the trial were USA, Canada, France, Germany, Finland, Netherlands – crosswalk value sets were not available for Canada or Finland.

3.2.5.2 Key efficacy results from supporting studies: TONES 1 and TONES 5

TONES 1

The CS provides a narrative summary of efficacy outcomes assessed at week 4 in the phase II TONES 1 RCT (ESS, MWT, CGI-c and PGIc). All participants in TONES 1 at this timepoint randomised to solriamfetol were receiving the 150 mg dose Endpoints measured after week 4 are not considered in the CS as patients were on the unlicensed 300 mg dose during this time.

Statistically significant improvements were reported at for solriamfetol 150 mg vs placebo for the following endpoints (full results are presented in CS Section B.2.6.2):
Mean change in ESS score from baseline [redacted] ([redacted] for solriamfetol 150 mg vs -[redacted] for placebo, [redacted])

- Mean change from baseline in average sleep latency (from first four trials of a five-trial MWT) at week 4 in the solriamfetol 150 mg arm was 9.5 (SE 1.3) minutes versus 1.4 minutes (SE 1.1) in the placebo arm (p<0.0001).

- % of patients improved on either the PGI-c or CGI-c (categories of 'minimally', 'much' or 'very much' improved) were statistically significantly higher in the solriamfetol 150 mg arm than the placebo arm (PGI-c 82.5% vs 44.4% respectively, p=0.0003; CGI-c 80.0% vs 51,1% respectively, p=0.0066).Improvements ESS, CGI-c and PGI-c were observed from week 1 onwards.

Efficacy results from TONES 1 are coherent with TONES 2 but do not contribute directly to the company's economic model.

TONES 5

TONES 5 (CS Section B.2.6.3) was a longer-term (up to 1 year) open-label study enrolling patients with narcolepsy (N=226) who had participated in previous solriamfetol trials (including TONES 1 and TONES 2). TONES 5 also enrolled patients with OSA who are not reported on in the current CS. The CS reports results from the open-label phase of this study (CS Section B.2.6.3.2) and from the two-week randomised withdrawal phase (CS Section B.2.6.3.3).

Open label phase

Improvements with respect to the baseline in TONES 2 for patients in Group A or with respect to the TONES 5 baseline for patients in Group B in the following outcomes were observed among participants with narcolepsy:

Improvements in ESS were observed from week 2 of treatment for both solriamfetol doses and were maintained over time (Table 13). These results have been used to support the assumptions in the company's economic model (see section B.3.2.2). Mean change from baseline ESS at final assessment: ranged from [redacted] (Group A) to [redacted] (Group B) for the 75 mg dose and [redacted] to [redacted] for the 150 mg dose relative to baseline. The ERG notes that only [redacted] of enrolled narcolepsy patients (N=226) contributed to these analyses (company response to clarification question A15). Although not explicitly stated it is likely the remaining participants of TONES 5 received the 300 mg solriamfetol dose. The CS reports data for the combined solriamfetol doses (including 300 mg) in CS Figures 7 and 8 and text in CS Section B.2.6.3.2.1.

Table 13 TONES 5 Change in mean ESS scores from baseline for patients with narcolepsy for the solriamfetol 75 mg and 150 mg dose (Safety population)

	Group A		Group B	
	75 mg (n=10)	150 mg (n=55)	75 mg (n=5)	150 mg (n=8)
Change from baseline[a] at week 2	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline[a] at week 40	[redacted]	[redacted]	NA	NA
Change from baseline[a] at week 52	NA	NA	[redacted]	[redacted]

Source: CS Table 17 with numbers for each group from the company response to clarification question A15
Abbreviations: NA, not applicable; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Data presented as mean (SD).
[a] Baseline defined as the baseline of the parent study for Group A and baseline of TONES 5 for Group B.

- Improvement (categories of 'minimally', 'much' or 'very much improved) in PGI-c and CGI-c scores were observed to be maintained at each assessment, with improvement in >85% of patients at the final assessment.

[redacted] in HRQoL measures (FOSQ-10, SF-36v2, EQ-5D-5L Index and ΔEQ-VAS) relative to baseline [redacted] (CS Section B.2.6.3.2.3).

It should be noted that these effects were not controlled by a placebo group.

TONES 5 also included a randomised 2-week withdrawal phase (patients with narcolepsy randomised n=79). Patients randomised to continue solriamfetol treatment (75 mg, 150 mg and 300 mg dose groups combined) did not experience a big change in ESS indicating treatment benefit was maintained. Patients randomised to placebo (i.e. withdrawn from solriamfetol treatment) had a statistically significant mean increase in ESS from the beginning to the end of the withdrawal phase indicating a worsening of daytime sleepiness [[redacted] for solriamfetol vs placebo respectively; between-group difference: [redacted] ([redacted]]). PGI-c and CGI-c scores were reported to worsen in the placebo group ([redacted] of patients respectively) compared to those in the solriamfetol group ([redacted] respectively). Mean FOSQ-10 scores were also reported to be [redacted] in the placebo group compared to solriamfetol [[redacted], between-group difference: [redacted], CS Section B.2.6.3.3.3).

3.2.5.3 Sub-group analyses

Pre-specified sub-group analysis analyses for each trial are listed in the final row of CS Table 4. In this section we report only on TONES 2 trial sub-group analyses. Results for TONES 1 and TONES 5 sub-group analyses are reported in CS sections B.2.7.2 and B.2.7.3 respectively. For all subgroup analyses, interaction tests were not performed. The ERG note that these analyses are under-powered to detect a statistically significant difference within and between sub-groups.

TONES 2

In TONES 2 the prespecified subgroups listed in CS Table 4 are presence or absence of cataplexy, region (North America and Europe) and Country (e.g. US, Canada, Finland, France, Germany Italy). In response to clarification question A1 the company provided a subgroup analysis of ESS for patients with and without prior modafinil use. In this section we report on the subgroup analyses by cataplexy status, region and prior modafinil use.

Cataplexy status

Randomisation in TONES 2 was stratified by cataplexy status and this subgroup analysis was prespecified because of the theoretical potential that EDS may differ between narcolepsy patients with and without cataplexy (response to clarification question A7). Results from the cataplexy sub-group analyses in TONES 2 are described in CS Section B.2.7 and CS Appendix E and are summarised below in Table 14. Similar improvements in the change in ESS relative to placebo were seen in patients with/without cataplexy for the 150 mg solriamfetol dose at week 12. The mean difference in the change in MWT relative to placebo appeared to be of higher magnitude in patients without cataplexy (9.06 minutes) versus those with cataplexy (6.07 minutes), although this difference in MWT may not be of clinical relevance and 95% confidence intervals were wide and overlapping. Similarly, although [redacted]. Although formal tests of interaction were not conducted, a differential response in patients with/without cataplexy remains possible.

Table 14 Subgroup analysis in TONES 2: cataplexy status

Outcome	With Cataplexy N=87[a]	Without Cataplexy N=85[b]
Change in ESS (95% CI) at week 12		
75 mg vs placebo	-1.3 (-3.9 to 1.3)	-3.0 (-5.6 to -0.4)
150 mg vs placebo	-3.7 (-6.4 to -1.1)	-3.7 (-6.3 to -1.2)
Change in MWT (95% CI) at week 12 (minutes)		
75 mg vs placebo	1.63 (-3.60 to 6.86)	3.43 (-1.85 to 8.70)
150 mg vs placebo	6.07 (0.74 to 11.40)	9.05 (3.83 to 14.27)
PGI-c, difference in % improved (95% CI) at week 12		
75 mg vs placebo	10.0 (-15.18, 35.20)	47.7 (25.29, 70.03)
150 mg vs placebo	33.0 (9.00, 56.90)	44.1 (21.06, 67.12)

Source: CS Appendix E.1, Table 86, [redacted]
[a] mITT hence [redacted] from the solriamfetol 150 mg arm with cataplexy are missing from these data.
[b] mITT hence [redacted] from the placebo arm without cataplexy and [redacted] from the solriamfetol 150 mg arm without cataplexy are missing from these data.

Region

In TONES 2 sub-group analyses by region suggested that results for North America were [redacted] (CS Appendix E).

Prior Modafinil Use

The company response to clarification question A1 (Figures 1 & 2) provided additional results from TONES 2 stratified by prior modafinil use. The company reported that no 'hangover' pharmacological effect would be expected in patients with prior use of modafinil due to the wash-out period imposed in TONES 2. The ERG notes that the extent of prior modafinil use (or indeed stimulants) could be considered a proxy for treatment stage which may influence future treatment response, for example, if patients with long-standing disease adapt their behaviour. Nevertheless, the sub-group analysis did not reveal any marked difference in response between those who had and had not previously used modafinil.

3.2.5.4 Adverse events

Adverse event data from the three TONES trials are summarised in CS Section B.2.10. [redacted]. The ERG notes that long-term safety data from TONES 5 for the solriamfetol doses of interest (75 mg and 150 mg) in patients in patients

with narcolepsy is limited because there were only [redacted] patients on the 75 mg dose and [redacted] patients on the 150 mg dose, the remainder ([redacted]) received the unlicensed 300 mg dose of solriamfetol. Mean (SD) treatment exposure in the narcolepsy population was [redacted] days ([redacted]) for all doses combined but less for the 75 mg ([redacted]) days) and 150 mg ([redacted] days) doses.

Across all three trials, AEs were generally non-serious (Table 15) with the highest incidence of discontinuation due to AEs reported in the longer-term TONES 5 study (10.2%; all doses combined). Patients randomised to solriamfetol in TONES 2 had [redacted] of treatment-related AEs compared to placebo ([redacted]%) with [redacted] observed for 150 mg ([redacted]%) versus 75 mg ([redacted]%). Across the three studies eight patients with narcolepsy (all in solriamfetol groups) experienced serious AEs, including one [redacted] in the TONES 5 study that was considered related to treatment by the study investigators. No deaths were reported in narcolepsy patients.

Table 15 Adverse events reported in TONES trials in narcolepsy patients

Type of AE	Number of patients with AE (%)					
	TONES-2 (Week 12)			TONES-1 (Week 4)		TONES-5
	Placebo (N=59)	Sol 75 mg (N=59)	Sol 150 mg (N=59)	Placebo (N=49)	Sol 150 mg (N=44)	All doses combined (N=226)[a]
Any AE	27 (45.8)	34 (57.6)	47 (79.7)	29 (59.2)	27 (61.4)	169 (74.8)
Any treatment-related AE	[redacted]	[redacted]	[redacted][b]	[redacted]	NR	[redacted]
Serious AE	0	0	1 (1.7)	0	1 (2.3)	6 (2.7)
Any treatment-related serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE's leading to study/drug discontinuation	1 (1.7)	1 (1.7)	3 (5.1)	2 (4.1)	2 (4.5)	23 (10.2)
Deaths	[redacted]	[redacted]	[redacted]	0	0	0

Source: Compiled by the ERG from data presented in CS Tables 33-35 and CSRs for TONES 2 and TONES 1
NR not reported
[a] narcolepsy sub-population.
[b] CS table 33 reports 34 events but this would not equate to 44.1% in a group of 59 patients. The CSR reports [redacted] which seems likely to be the correct value.

CS Tables 33-35 present the most commonly reported AEs. The most frequently reported AE was headache in all three studies although the incidence varied from approximately 5-10% in those receiving placebo, approximately 10-24% in those receiving either 75 mg or 150 mg solriamfetol and approximately 14% in Tones 5 for the 75 mg/150 mg/300 mg solriamfetol doses combined. Nausea, decreased appetite, anxiety and insomnia were also

listed among the most frequent AEs in all three studies.

[redacted] AEs of special interest are discussed in Table 16.

Table 16 Adverse events of special interest

Adverse event of interest	Concern	Main finding
Insomnia	Solriamfetol is a wake-promoting agent	In TONES 2 and TONES 5 insomnia events [redacted] with a small number leading to study withdrawal ([redacted] in TONES 5, n=0 in TONES 2).
Depression & suicidal ideation	Depression is a common comorbidity in the target population with narcolepsy.	• AEs associated with depression were reported [redacted] (CS Section B.2.10.3.2) in TONES 2 ([redacted]). [redacted] • In TONES 5 (CSR Table 14.3.1.19.2), [redacted] in the narcolepsy sub-population (of which [redacted]% and [redacted]% were patients receiving solriamfetol 75 mg and 150 mg respectively) experienced an event classified within an event cluster defined as 'Depression and Suicidality'[a]). [redacted]. • Overall, there was no evidence to suggest an association between solriamfetol and an increased risk of suicidal ideation from the TONES trials.
Cardiovascular events	Patients with narcolepsy may have comorbidities such as hypertension, obesity and diabetes which are major risk factors for cardiovascular events.[3]	• A small number of cardiovascular AE were reported in TONES 2 (CS Section B.2.10.3.3) including one serious case (non-cardiac chest pain) that was considered unrelated to treatment. Palpitations were reported more frequently for solriamfetol 150 mg (n=3, 6.8%) versus placebo (n=1, 2.0%) in TONES 1 and in TONES 2 (solriamfetol 150 mg [redacted]). • Small dose-dependent changes in mean heart rate and blood pressure were observed in TONES 2 at week 12.

Adverse event of interest	Concern	Main finding
Abuse/withdrawal potential	Potential risk associated with drug class (centrally acting sympathomimetic drugs	• No evidence of rebound hypersomnia was observed when patients abruptly switched to placebo after 6 months of treatment in the withdrawal phase of TONES 5. • In a separate study in users of recreational drugs, solriamfetol (doses ≥300 mg) was observed to have a higher abuse potential when compared with placebo but similar or lower abuse potential when compared with a positive control, phentermine (an amphetamine-related stimulant considered to have low abuse potential).[18]

[a] includes reports of 'Depression', 'Depressive symptom', 'Depressed mood', 'Inappropriate affect', 'Suicide attempt'.

The ERG notes that the safety of solriamfetol in patients with significant cardiovascular disease could not be assessed as these patients were excluded from the TONES trials and as such the drug is contra-indicated for use in patients with unstable or serious cardiovascular disease.

3.2.5.5 Other outcomes used in economic model

The economic model uses additional data form TONES 2 and TONES 5 to estimate discontinuation rates due to lack of efficacy.

In TONES 2, discontinuation rates due to lack of efficacy at week 12 were:

- 1.7% (1/58) for the placebo arm
- 6.8% (4/59 patients) for the 75 mg dose arm
- 1.8% (1/55) for the 150 mg dose

This did not appear to be dose-dependent (CS Appendix D.2.1). For all solriamfetol patients in TONES 2 (including the unlicensed 300 mg dose arm), the overall discontinuation rate due to lack of efficacy of 6.4% (11/173 patients) at week 12 has been used to estimate discontinuation due to lack of efficacy in the initiation phase of solriamfetol treatment in the company's base case economic model (section 4.2.6 of this ERG report).

In TONES 5, the discontinuation rate due to lack of efficacy for all three doses of solriamfetol combined was 17.3%. The company have subtracted the rate assumed in the initiation phase (6.4%) from that observed in TONES 5 (17.3%) to provide an ongoing rate of discontinuation due to lack of efficacy in the longer-term maintenance phase of treatment for the economic model.

3.2.6 Meta-analysis of company study results

No meta-analyses of data from the solriamfetol versus placebo RCTs are presented in CS B.2.8. Instead the company has conducted indirect treatment comparisons via network meta-analysis (NMA). A summary of the NMA methods and some of the results are presented in CS Document B (CS section 2.9) with additional details of the methods and further results presented in CS Appendix D.

3.3 Critique of studies identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 Rationale for ITC

The company identified no head-to-head comparisons of solriamfetol against any of the comparators listed in the NICE scope (dexamphetamine, methylphenidate, sodium oxybate and pitolisant). Therefore, an indirect treatment comparison using NMA was undertaken to provide estimates of relative clinical effectiveness that could be used to inform the health economic model.

3.3.2 Identification, selection and feasibility assessment of studies for ITC

The company conducted a systematic literature review (SLR) to identify evidence for the ITC. The search strategies are reported in Appendix D, sections D.1.1 and D.1.2 (see section 3.1 of this report for a summary). The initial searches were limited to identify RCTs.

The inclusion and exclusion criteria for the ITC are reported in CS Appendix D.1.3, Table 1 and the processes for screening references and data extraction in CS Appendix D.1.3.1(see section 3.1 of this report for a summary).

The SLR identified 11 unique references reporting a total of seven RCTs that met the inclusion criteria for the ITC (Table 17). These RCTs evaluated the following treatments from the NICE scope for this appraisal: solriamfetol, pitolisant, modafinil and sodium oxybate.

Table 17 Included studies/citations for the ITC from the RCT search

Author, Year	Comparisons (length of follow-up)
Solriamfetol studies	
TONES 2[a] [19]	Solriamfetol 150 mg vs Solriamfetol 75 mg vs Placebo (12 weeks)
TONES 1[a] [20]	Solriamfetol 150 mg (weeks 1-4) increasing to 300 mg (weeks 5-12) vs placebo
Pitolisant studies	
Dauvilliers, 2013[a] [21]	Pitolisant 10-40 mg vs modafinil 100-400 mg vs placebo (8 weeks)
Szakacs, 2017[a] [22]	Pitolisant 5-40 mg vs placebo (7 weeks)
Sodium oxybate studies	
Xyrem, 2002[a] [23] Bogan, 2015[b] [24]	Sodium oxybate 3 g vs Sodium oxybate 6 g vs Sodium oxybate 9 g vs placebo (4 weeks)
Xyrem, 2005[a] [25] Xyrem® International Study Group, 2005[b] [26] Bogan, 2016[b] [27] Weaver, 2006[b] [28]	Sodium oxybate 4.5 g vs Sodium oxybate 6 g vs Sodium oxybate 9 g vs placebo (8 weeks)
Black, 2006[a] [29]	Sodium oxybate 6-9 g vs modafinil 200-600 g vs sodium oxybate + modafinil vs placebo (8 weeks)

Source: Based on information presented in CS Appendix D Table 3 but extensively edited by the ERG
Abbreviations: TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
[a] Designated as the primary reference for this study in the CS.
[b] Designated as the secondary reference in the CS.

We identified that the search strategy did not appear to have picked up all the modafinil and pitolisant studies that had been identified in two published meta-analyses identified in the CS. [30,31] The company were asked to clarify whether four modafinil RCTs and a publication reviewing pitolisant treatment studies by the European Medicines Agency (EMA) had been considered for inclusion in their systematic review (clarification question A18). They responded that their search had identified these five studies but they had all been excluded for the reasons given in Table 6 within their response to clarification question A18. The ERG agrees that it was appropriate to exclude the four modafinil studies.[32-35] The excluded EMA review of the pitolisant trials,[36] however, includes details of an unpublished pitolisant trial, the Harmony Ibis RCT, which compared pitolisant versus both modafinil and placebo. We found additional details about this study, including its inclusion criteria, patient characteristics, patient numbers per arm and baseline ESS and MWT, from the European Public

Assessment Report (EPAR) for pitolisant and/or the clinical trials record for the Harmony Ibis RCT (NCT01638403). Baseline characteristics, where reported, were similar to the other included studies (see Appendix 2). We therefore consider it inappropriate to exclude this pitolisant trial and we have updated the company's NMA to include this trial (where possible) in the networks of evidence that inform the economic model (described further in Section 3.6 of this ERG report).

No RCT evidence for stimulant treatments (such as the comparators dexamphetamine or methyphenidate) was identified. Therefore, the company performed an additional search, not limited by study design, to identify all types of study in which dexamphetamine, methyphenidate or amphetamine were used in adults with narcolepsy. The screening criteria for these search results are reported in CS Appendix D.1 Table 2 and the methods used for screening reported in CS Appendix D.1.3.2. Seventeen citations were identified through eligibility screening but none of these could be included in the ITC predominantly (n=13) because they did not include an outcome analysed in the ITC (CS Appendix D.1.3.4 Table 5). The four studies that did include a relevant outcome are summarised in CS Appendix D.1.4.2 but none of these provided data that could be incorporated in the ITC network. Expert clinical advice given to the ERG agrees with the company that the market share for dexamfetamine and methylphenidate is declining, with one expert commenting that neither drug had been rigorously trialled in the adult narcolepsy population. Although stimulant treatments are not included in the company's base case cost effectiveness analysis, the company did conduct a scenario analysis based on hypothetical changes in ESS relative to solriamfetol (see Section 5.2.3 of this ERG report).

3.3.3 Clinical heterogeneity assessment

The company do not report conducting a feasibility assessment in support of their decision to conduct an NMA. However, to enable assessment of potential clinical heterogeneity the CS presents tables of baseline patient characteristics (CS Appendix D Tables 17 and 18) and CS Appendix D Table 8 provides some details on the methods of the seven included RCTs.

The aims and the primary outcomes of the seven RCTs available for ITC differed. Five RCTs (TONES 2, TONES 1, Dauvilliers, Xyrem 2005 and Black) were primarily interested in the treatment of excessive daytime sleepiness and impaired wakefulness whereas the other two RCTs (Szakacs and Xyrem 2002) were primarily interested in the treatment of cataplexy. Among trials of the same treatments there were differences in drug doses. The range of pitolisant doses in the Dauvilliers and Szakacs RCTs differed as did the range of the

modafinil doses in the Dauvilliers and Black RCTs (Table 17). There were also differences in treatment duration (Table 17).

Although the company states in Appendix D section D.1.5.1 “No apparent or potential differences in the underlying disease of patient populations was identified” no information about how narcolepsy was defined and/or confirmed in each RCT was presented. In response to clarification question A23 the company tabulated some additional information about the patients enrolled in each RCT included in the NMA. This shows that the majority of studies (n=5) required patients to be diagnosed with narcolepsy according to International Classification of Sleep Disorders (ICSD) criteria. In the other two trials the criteria for diagnosing narcolepsy were either the American Sleep Disorders Association (ASDA) criteria (n=1) or an overnight polysomnography (PSG) and multiple sleep latency test (MSLT) as well as current symptoms (n=1). Four RCTs [19-22] required patients to have a particular minimum ESS score (ranging from a minimum of 10 in the two TONES RCTs to 14 in the Dauvilliers RCT). The trials included in the NMA varied in terms of those that did not allow any concomitant therapy[19,20,29] and those that did.[21-23,25]

The CS does not include any information on the baseline severity of patients in the trials, as measured by the clinician global impression of severity (CGI-s) or an alternative scale. The company was asked to provide these data (Clarification question A29) but the only trials which reported numerical values for the CGI-s were the TONES 2 and Xyrem 2005 RCTs. The data provided are difficult to compare because of differences between these two trials in the reporting categories (the TONES 2 CGI-s reports seven categories of severity but the Xyrem 2005 RCT reports only six categories for the CGI-s (omitting ‘Severely ill’).

We identified some errors in the company’s tables of baseline characteristics (CS Appendix D Table17 and Table 18). These errors included data from the TONES 1 RCT being entered out of step with the table row headings (Clarification question A28) and there was also uncertainty about the proportions of patients with cataplexy being reported for Black 2006 because this information could not be identified by the ERG in the published paper (Clarification question A 30). In addition, the ERG also identified errors in the baseline data extracted from the Szakacs 2017 paper (an RCT of pitolisant versus placebo).

After correcting the errors in CS Appendix D Table 17 and Table 18 and receiving clarification from the company regarding the data for Black 2006, we found the following differences between the participants in the trials included in the NMA:

Cataplexy: In three RCTs (Szakacs 2017, Xyrem 2002 and Xyrem 2005) all participants had to have boith cataplexy and narcolepsy to be enrolled. In the other four RCTs (TONES 1, TONES 2, Dauvilliers, Black) the presence of cataplexy was not an enrolment criterion, but varying proportions of patients enrolled had concomitant cataplexy. Approximately 80% of the Dauvilliers participants experienced cataplexy, whereas in TONES 2 the proportion was approximately 50% and in the TONES 1 RCT it was about a third of participants. In the Black 2006 RCT the proportion of participants differed between the two arms that were included in the NMA (28% with cataplexy in the sodium oxybate 6-9 g arm and 58% in the placebo arm).

Concomitant medication: In the Xyrem 2002 RCT and the Xyrem 2005 RCT participants were permitted to take stimulants for the treatment of excessive daytime sleepiness. In the other five RCTs participants were not taking concomitant stimulants, either because no concomitant therapy was permitted (TONES 2, TONES 1, and Black) or because only anti-cataplectic medication (sodium oxybate or antidepressants) was permitted (Dauvilliers and Szakacs).

ESS: Despite the differences in the trials' inclusion criteria for ESS, the mean or median baseline ESS scores of participants were fairly homogeneous, typically between 17 and 19. The exception was the Black RCT where median ESS scores were between 14 and 16 across the four arms of this trial, indicating participants in this group may have had less severe EDS than in the other trials.

MWT40: Not all studies reported baseline MWT40 values but it was notable that in the Szakacs RCT the values were lower (geometric means 4.1 and 3.5 minutes in the placebo and pitolisant arms respectively) in comparison the Dauvilliers RCT which also reported geometric mean values (7.4 to 8.8 minutes across three arms) and in comparison to the TONES 1 and TONES 2 studies which reported mean values of 5.7 to 7.9 minutes across the arms of both studies.

For other characteristics reported (e.g. age, sex, BMI) the trials appear similar.

ERG conclusion on heterogeneity among ITC studies

Overall the ERG finds that there are a variety of sources of clinical heterogeneity between the studies included in the company's ITC. We do not believe that this heterogeneity is sufficient to prevent an ITC being conducted, but it does suggest that a random-effects analysis is preferable to fixed-effect.

3.3.4 Similarity of treatment effects

The similarity of treatment effects (meaning that the included trials are similar for modifiers of relative treatment effect) is a key assumption underlying any ITC.[37] The company used internal expert opinion to establish that cataplexy (and the related use of concomitant medication) was a potential treatment effect modifier. In response to clarification question A7 the company states that there may be a theoretical potential for patients with narcolepsy and cataplexy to have differing amounts of EDS compared to those with narcolepsy alone. Similarly, people with narcolepsy and cataplexy might respond differently to a wake-promoting treatment. Consequently, in the TONES 2 trial randomisation was stratified by the presence of absence of cataplexy and a subgroup analysis by the presence or absence of cataplexy was pre-specified. In response to clarification question A27 the company indicate that "*No information was gathered from UK Clinical Expert opinion which contradicted this view*" that cataplexy and the related use of concomitant medication was a potential effect modifier. Where possible the company conducted ITC scenario analyses to explore the impact of cataplexy and use of concomitant therapy.

3.3.5 Risk of bias assessment for RCTs included in the ITC

Risk of bias assessments were undertaken for each of the RCTs included in the ITC (CS Appendix D.1.5.4). We conducted our own risk of bias and quality assessment for the solriamfetol trials (see section 3.2.2) and for the comparator RCTs (including the Harmony Ibis trial where our judgements were based on information available in the pitolisant EPAR[38]). Overall our judgements were in broad agreement with the company's judgements (a summary table is provided in Appendix 4), apart from the following:

- Most studies were assessed by the company as including an ITT analysis. Strictly, the comparator trials included modified ITT (mITT) analyses as they typically included all randomised patients who took at least one dose of randomised medication and had a baseline and at least one post-baseline efficacy measurement. Where reported, the proportion of excluded from the mITT was small (<5%) and therefore unlikely to introduce any bias.
- Discontinuation rates were mis-reported in the CS (Section D.1.5.4, Table 22) for the Szackacs study where 9% of pitolisant and 18% of placebo patients discontinued (the CS reported these percentages in opposite)
- The company did not assess the handling of missing data. The ERG performed this assessment and found that only one study (Dauvilliers) had conducted a sensitivity analysis to show that their analyses were robust to different methods of imputing missing values. In the remaining studies, the impact of missing data was unclear as

the proportions of missing data were not reported, the imputation methods were not described or were limited to a single imputation method such as 'last observation carried forward'.

ERG conclusion on the studies included in the indirect treatment comparison

The literature search for the company's ITC was well conducted but not fully documented with five studies not listed as having been identified. The ERG disagreed with the exclusion of one of these studies (Harmony Ibis). The trials differed in their primary aim (treatment of EDS or treatment of cataplexy) and there were differences in the proportions of participants with cataplexy across the trials (and also therefore the use of concomitant anti-cataplexy medication). Cataplexy has been identified by the company's clinical experts as a potential treatment effect modifier in narcolepsy. Despite some clinical and methodological heterogeneity between the trials the ERG accepts that the degree of heterogeneity does not preclude conducting the NMAs.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company's methodological approach to the NMA is presented in Appendix D.1.5.

A series of 12 separate NMAs, each linking treatments via a common (placebo) comparator, were undertaken for 10 outcome measures (ESS, MWT20, MWT40, SF-36 PCS, SF-36 MCS, PGI c, CGI c, incidence of any TEAE, incidence of serious TEAEs and incidence of discontinuation due to TEAEs).

Although a total of seven trials met the inclusion criteria for the ITC, not all provided data for each outcome, hence the number of trials included in the individual NMAs varied (from 2 to 6).

The trials varied in length of treatment and follow-up outcome assessment, from 4 to 12 weeks. The NMAs assessed effectiveness outcomes at 8 weeks follow-up. For two of the effectiveness outcomes (ESS and MWT40) NMAs were conducted for two separate follow-up timepoints:

- ESS change from baseline at 4 weeks NMA (six studies) and ESS change from baseline at 8 weeks NMA (five studies).
- MWT40 change from baseline at 4 weeks NMA (two studies) and MWT40 change from baseline at 8 weeks (four studies)

The NMAs report changes since baseline for effectiveness outcomes and incidence for TEAEs and discontinuation due to TEAE.

Scenario analyses were also conducted to explore alternative parameters:

- using TONES 2 12-week data (ESS, MWT20 and MWT40 outcomes)
- impact of concomitant stimulant therapy in sodium oxybate trials (ESS week 4, ESS week 8, MWT40 week 8, Serious TEAE, discontinuation due to AE outcomes)

Only one NMA provides direct data inputs to the economic model - the ESS change from baseline at 8 weeks (Figure 1), based on data from five trials. The other outcomes for which NMAs were conducted are described as 'supporting endpoints' by the company (we infer this means they support some of the assumptions made in the economic evaluation) but their data do not directly inform the economic model.

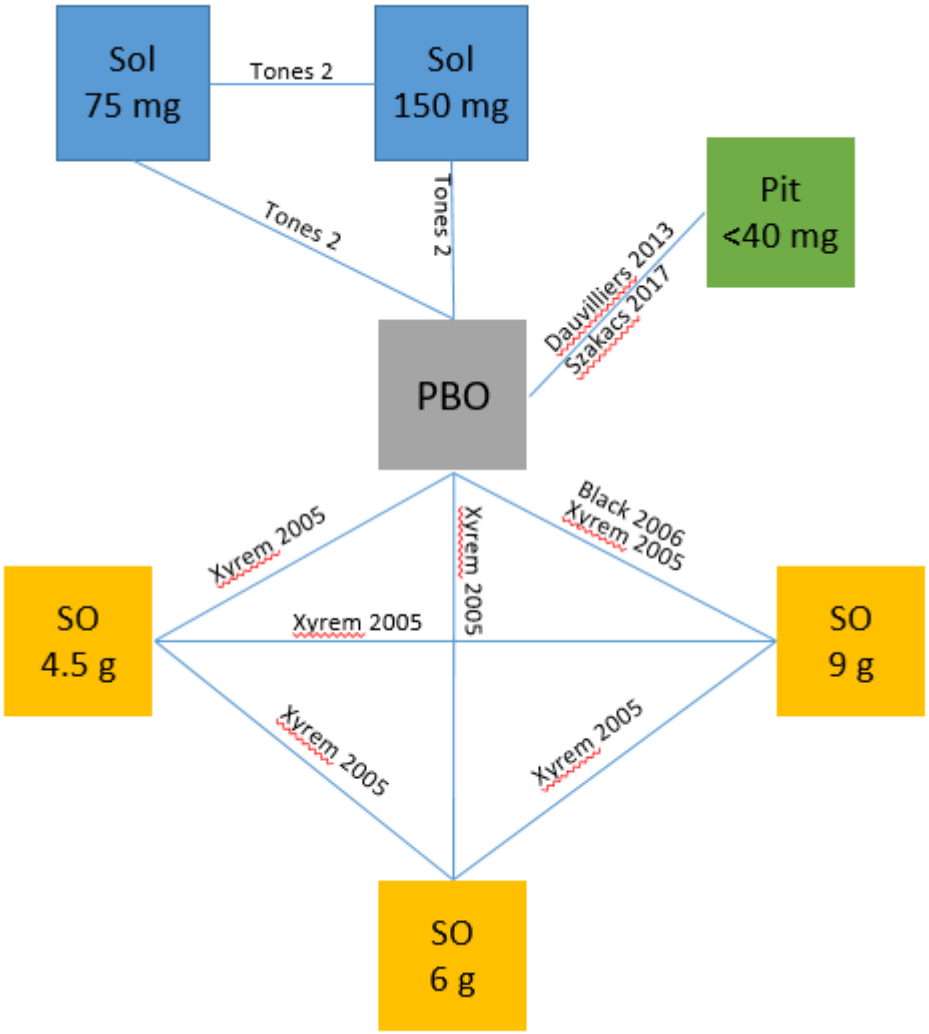

Figure 1 ESS 8-week NMA network diagram

Abbreviations: PBO – placebo; Pit – pitolisant; SO – sodium oxybate; Sol - solriamfetol

3.4.1 Data inputs to the NMA

Two of the RCTs included by the company (Dauvilliers 2013 and Black 2006) included modafinil treatment arms that were omitted from the NMA. As we have discussed earlier, the company does not consider that modafinil would be a relevant alternative to solriamfetol in clinical practice and thus they have excluded it from their decision problem. However, one of the reasons modafinil was included in the company's SLR was in the event that it "might lead to any additional connections of comparators of interest and add strength to the overall network" (CS Appendix D section D.1.3.1). In response to clarification question A21a the company explained that they had excluded these modafinil arms from the ITC because the variable dose arms differed between the two trials (100-400 mg once daily and 200-600 mg once daily, Dauvilliers 2013 and Black 2006, respectively). This issue of pooling doses is the subject of debate in the narcolepsy literature; whilst a previous published NMA pooled doses across modafinil arms (Lehert 2018[31]), subsequent correspondence argued against this (Snedecor, 2019[39]). (We note that the Lehert 2018 NMA was funded by the manufacturer of pitolisant and the authors of the Snedecor, 2019 correspondence were consultants to the manufacturer of solriamfetol).

We asked the company to update their NMA to include the modafinil arms of the trials by Dauvilliers 2013 and Black 2006, and include modafinil arms from any other relevant RCTs identified from the previous published meta-analyses (clarification question A21b). The company declined to update their NMA citing a numerical difference in ESS and CGI-c outcomes for the 200 mg and 400 mg modafinil doses. The ERG's view is that the aforementioned Harmony Ibis trial can be included in the NMA, and the 100-400 mg modafinil arms of the Dauvilliers 2013 and Harmony Ibis trials can be included to strengthen network connectivity. We have updated the company's NMA to include these modafinil arms where data were available to do this, based on the approach of not pooling modafinil dose arms (see Section 3.6 of this ERG report).

The use of imputation to calculate missing standard errors has introduced additional uncertainty into the analysis, particularly for sodium oxybate where no standard errors were reported in the original publications. In this case, these were estimated from the standard errors observed across the other studies and treatments. However, between-study heterogeneity may introduce heterogeneity of standard errors between studies. More

complex methods of imputation were excluded by the ERG due to the lack of reporting of standard errors for any of the sodium oxybate studies.[40]

The ERG checked the data inputs to the key NMA that informs the health economic model base case, ESS at 8-weeks (presented in CS Appendix D Table 9). We identified several errors and inconsistencies in the extracted data (details of these are provided in Appendix 5). We have corrected these errors in an update to this NMA (see Section 3.6 and Appendix 6 of this ERG report).

3.4.2 Statistical methods for the NMA

The NMA was conducted according to a Bayesian approach using WinBUGS software (v1.4). Both fixed- and random-effects analyses used vague prior probability distributions (priors). The model used a burn-in of 10,000 simulations followed by a further 200,000 inference iterations for parameter estimation. All models were evaluated for convergence and model fit was assessed across two parameters (total residual deviance and the deviance information criterion [DIC]). The WinBUGS code for the binary fixed effect, binary random effects, continuous fixed effect and continuous random effects models is provided in Appendix D.1.5.3. Although the binary code was derived from the NICE Decision Support Unit (DSU) Technical Support Document 2 code,[41] the use of certain indices (*noGoodTx* & *txNums*) to describe the data in the binary code was unclear hence the ERG used the DSU code.

The NMA results are presented in different locations: CS Section B.2.9.2 reports the ESS week 4 and week 8 NMA outcomes, briefly summarises the MWT and safety outcomes, reports the NMA scenario analysis using the 12-week solriamfetol ESS data and briefly summarises the other NMA scenario analyses. CS Appendix D.1.5.5 reports detailed results for the MWT and safety NMAs and the other scenario analyses.

The ERG validated the NMA using DSU code[41] and CS input data from CS Appendix D Table 9 (for ESS change from baseline at 8 weeks) & clarification question response A31 Table 17 (for ESS scenario analysis with 12 week solriamfetol data). Relative treatment effects were generally consistent (differences <0.05) apart from those for pitolisant which differed by 0.1 in the fixed effects (Appendix 7). These differences persisted when the ERG used the CS code and may be indicative of an error in the CS input data, Monte Carlo error, or possibly the high imputed standard error for the Dauvilliers pitolisant arm.

In several of the NMAs, including the ESS 8-week network (Figure 1), there are closed loops of evidence which have both direct and indirect evidence for the sodium oxybate trials. The CS however, states that consistency evaluation "*was not feasible due to lack of "closed loops" of evidence*" (CS Appendix D.1.5.2). The company were asked to examine inconsistency (clarification question A20) which they did for the two networks where this was feasible, ESS (week 4 and week 8, six RCTs and five RCTs respectively) and discontinuations due to AEs (five RCTs). In their response to clarification question A20 the company note that the residual deviances of the base case and inconsistency NMA models are similar and lie on a diagonal line, which indicates consistency. However, they point out that this is likely due to the small number of studies included in the analyses. The ERG could not fully understand the company's consistency/inconsistency plots which appear to present data at the study level in contrast to the trial arm level methodology as described in NICE DSU TSD 4.[42] The plots also show a different number of trials between the ESS and TEAE discontinuation results despite the networks being identical. Nevertheless, the ERG agrees with the company's conclusion that inconsistency between direct and indirect evidence is not present.

3.4.2.1 Choice between random effects and fixed-effect models

The company's preference was to use the results of the fixed-effect analyses for the following reasons:

- Very similar or slightly lower DIC for the fixed-effect analyses
- Lack of significant (clinical) heterogeneity
- A small evidence base with the majority of networks being formed with only one trial per pairwise comparison.

The company reports the model fit statistics (including DIC and total residual deviance) for each network (CS Tables 22 and 26 and CS Appendix D Tables 27, 31, 35, 39, 43, 47, 50, 54, 58, 62, 66, 70, 74 and 78). For 11 networks the DIC is lower for the fixed effect model and for five networks it is lower for the random effects model. In the majority of cases the DIC values are similar for the fixed and random effects models but for two networks, MWT40 week 4 and any TEAE, the differences are greater (the random effects model DIC being 4.15 and 5.843 points lower respectively than the fixed-effect model DIC, indicating a better model fit). The ERG notes, however, that neither the MWT40 week 4 nor the any TEAE network results contribute data to the economic model. In situations where there is at least some clinical heterogeneity and there is no meaningful difference in DIC, the ERG would prefer to use the random effects model.

In addition to reporting the model fit statistics the company also report the results of statistical heterogeneity testing for the outcomes where there were at least two RCTs that reported the same pairwise comparison (CS Appendix D Table 19 and Table 20). The I^2 value (which represents the quantity of heterogeneity) was 0% for eight of the 10 comparisons (i.e. no heterogeneity) and 0.2 for one comparison, whereas in the any TEAE network for the pitolisant ≤40 mg vs placebo comparison, the I^2 value suggests considerable heterogeneity (87.1%). For the any TEAE network in particular this supports the ERG's view that the random effects model is a more appropriate choice.

3.4.3 Summary of ERG critique of the NMA

The company reports 12 NMAs, between them assessing at total of 10 effectiveness and safety outcomes, in which active treatments are connected via a common (placebo) comparator. The largest networks were those for the outcome of ESS change from baseline at 4 weeks (six studies) and ESS change from baseline at 8 weeks (five studies). The results of this latter network directly inform the clinical effectiveness estimates in the economic model.

Three active treatments were included in the networks (where data allowed): solriamfetol (75 mg and 150 mg doses), pitolisant (<=40 mg) and sodium oxybate (3 g, 4.5 g, 6 g and 9 g doses). Modafinil was not included as the company do not consider this a relevant comparator to solriamfetol.

The company declined to update their NMAs to include modafinil treatment arms from the included RCTs, or modafinil arms from any other RCTs identified from published meta-analyses that would meet their SLR inclusion criteria. As already noted, the ERG would have included the unpublished Harmony Ibis trial (which compares pitolisant versus modafinil and placebo) and the modafinil arm from this RCT could have been included with the modafinil arm from the Dauvilliers RCT.

Some RCTs included in the NMA did not report standard errors and therefore values had to be imputed. The use of imputation to calculate missing standard errors has introduced additional uncertainty into the analysis, particularly for sodium oxybate.

The ERG's validation of the company's NMA produced relative treatment effects that were generally consistent with the company's apart from those for the comparison of solriamfetol

versus pitolisant. The differences may indicate an error in the CS input data, Monte Carlo error, or are possibly due to the high imputed standard error for the Dauvilliers trial pitolisant arm.

The company reports the model fit statistics (DIC) which, for the majority of networks, are similar for the fixed and random effects models. The company's preference is to use the results from the fixed-effect model. However, the ERG would prefer to use the random effects model in situations such as this where there is no meaningful difference in DIC but there is at least some clinical heterogeneity.

3.5 Results from the indirect comparison

In this section we focus only on those results which inform the company's base case economic model. Results that inform the ERG's economic model are presented in Section 3.6 of this ERG report.

3.5.1 ESS 8-weeks

The relative treatment effects obtained from the ESS 8-week NMA are used in the company's base case economic model (Section 4.2.6 of this report). The results from both the fixed effect and random effects models are reproduced in Table 18. The accompanying model fit statistics and rank probabilities for the fixed effects and for the random effects models are provided in CS Tables 26, 27 and 28 respectively. The absolute treatment effects show that all the treatments improved ESS (i.e. reduced the ESS score) with respect to baseline values. However, the lowest sodium oxybate dose in this analysis (4.5 g) improved ESS with a similar magnitude to placebo. When comparing the relative effects (fixed effect) of solriamfetol 150 mg to the other treatments in this network it can be observed that:

- Solriamfetol 150 mg provides an improvement (reduction) in ESS relative to placebo, solriamfetol 75 mg and sodium oxybate at a dose of 4.5 g as evidenced by the negative relative treatment effects and a credible interval that does not cross zero.
- Solriamfetol 150 mg provides a numerical improvement over the sodium oxybate 6 g dose but the credible interval crosses zero
- Solriamfetol does not provide a numerical improvement in ESS relative to sodium oxybate 9 g or pitolisant ≤40 mg but the credible intervals crossed zero in both cases and the numerical difference versus pitolisant is close to zero (0.050).

When comparing the relative effects from the random effects model (which is the ERG's preferred choice) the mean and median mean differences are very similar to those obtained

from the fixed effect model but the 95% credible intervals are much wider such that, in all comparisons, the credible interval crosses zero.

Table 18 ESS week 8 relative effects (as mean difference) and absolute effects

	Fixed Effects				Random Effects			
	Mean	Median	SD	95% CrI	Mean	Median	SD	95% CrI
Relative effects of solriamfetol 150 mg compared to treatment								
Placebo	-3.098	-3.099	0.848	(-4.761, -1.44)	-3.107	-3.108	2.094	(-7.589, 1.365)
Solriamfetol 75 mg	-1.797	-1.795	0.847	(-3.456, -0.137)	-1.798	-1.804	2.102	(-6.272, 2.719)
Pitolisant ≤40 mg	0.050	0.049	1.187	(-2.279, 2.377)	-0.038	-0.014	2.65	(-5.704, 5.47)
Sodium Oxybate 4.5 g	-2.946	-2.946	1.274	(-5.448, -0.447)	-2.974	-2.961	2.929	(-9.222, 3.226)
Sodium Oxybate 6 g	-1.946	-1.947	1.276	(-4.451, 0.558)	-1.965	-1.948	2.927	(-8.251, 4.236)
Sodium Oxybate 9 g	0.656	0.657	1.107	(-1.518, 2.823)	0.646	0.66	2.606	(-4.892, 6.175)
Absolute treatment effects								
Placebo	-1.359	-1.359	0.315	(-1.977, 0.741)	-1.349	-1.348	0.315	(-1.967, -0.736)
Solriamfetol 75 mg	-2.66	-2.663	0.809	(-4.242, -1.075)	-2.658	-2.662	2.094	(-7.213, -1.829)
Solriamfetol 150 mg	-4.457	-4.457	0.81	(-6.05, -2.871)	-4.456	-4.454	2.08	(-8.92, -0.001)
Pitolisant ≤40 mg	-4.507	-4.506	0.781	(-6.036, -2.973)	-4.417	-4.439	1.59	(-7.687, -1.021)
Sodium Oxybate 4.5 g	-1.511	-1.509	0.882	(-3.238, -0.225)	-1.482	-1.483	2.005	(-5.703, 2.782)
Sodium Oxybate 6 g	-2.51	-2.509	0.884	(-4.244, -0.777)	-2.49	-2.506	2.013	(-6.739, 1.78)
Sodium Oxybate 9 g	-5.113	-5.111	0.622	(-6.336, -3.9)	-5.101	-5.107	1.5	(-8.28, -1.901)

Source: Reproduction of CS Table 25
Abbreviations: CrI, credible interval; ESS, Epworth Sleepiness Scale; SD, standard deviation.
A negative absolute treatment effect represents an improvement (reduction) in ESS for a given treatment compared with baseline; a negative relative treatment effect represents an improvement (reduction) in ESS for solriamfetol 150 mg relative to the comparator.

The company conducted a scenario analysis for sodium oxybate to explore the impact of concomitant stimulant therapies. In this scenario only one of the three sodium oxybate trials was included (Black 2006) because this was the only sodium oxybate trial that did not allow concomitant stimulant therapy (Figure 2). The results are presented in Table 19 and they show that the findings for the relative effects of solriamfetol 150 mg were similar to the base case 8-week ESS NMA (Table 18). However, in both the fixed-effect and random effects models the sodium oxybate 9 g relative treatment effect reverses to become negative (i.e. solriamfetol now has a numerical improvement in ESS relative to sodium oxybate 9 g but the credible intervals cross zero as they did in the base case analysis). The ERG agrees with the company that, given the scenario includes only one sodium oxybate trial, it is not possible to make a clear judgement on the true impact of concomitant stimulant therapies in the sodium oxybate trials.

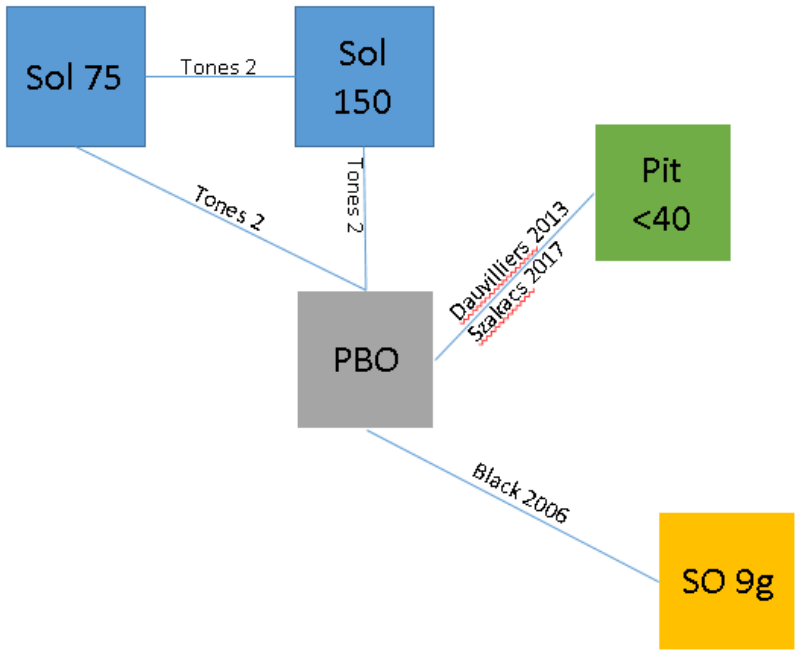

Figure 2 ESS 8-week NMA scenario: impact of concomitant therapy on sodium oxybate network diagram

Abbreviations: PBO – placebo; Pit – pitolisant; SO – sodium oxybate; Sol - solriamfetol

Table 19 Scenario: ESS week 8 relative effects (as mean difference) and absolute effects

	Fixed Effects				Random Effects			
	Mean	**Median**	**SD**	**95% CrI**	**Mean**	**Median**	**SD**	**95% CrI**
Relative effects of solriamfetol 150 mg compared to treatment								
Placebo	-3.095	-3.096	0.848	(-4.76, -1.436)	-3.108	-3.11	2.508	(-8.544, 2.299)
Solriamfetol 75 mg	-1.8	-1.8	0.85	(-3.471, -0.132)	-1.803	-1.8	2.497	(-7.229, 3.632)
Pitolisant ≤40 mg	0.049	0.051	1.193	(-2.28, 2.388)	-0.063	-0.029	3.137	(-6.917, 6.59)
Sodium Oxybate 9 g	-0.091	-0.093	1.323	(-2.683, 2.496)	-0.11	-0.104	3.584	(-7.835, 7.607)
Absolute treatment effects								
Placebo	-1.627	-1.628	0.349	(-2.31, -0.942)	-1.618	-1.617	0.351	(-2.305, -0.934)
Solriamfetol 75 mg	-2.922	-2.921	0.795	(-4.48, -1.362)	-2.923	-2.922	2.482	(-8.358, 2.482)
Solriamfetol 150 mg	-4.722	-4.723	0.796	(-6.282, -3.166)	-4.726	-4.727	2.49	(-10.16, 0.694)
Pitolisant ≤40 mg	-4.771	-4.772	0.758	(-6.257, -3.288)	-4.664	-4.691	1.843	(-8.533, -0.644)
Sodium Oxybate 9 g	-4.63	-4.63	0.932	(-6.456, -2.809)	-4.617	-4.626	2.537	(-10.11, 0.868)

Source: Reproduction of CS Appendix D Table 65

Abbreviations: CrI, credible interval; ESS, Epworth Sleepiness Scale; SD, standard deviation.

It was not possible for the company to include pitolisant in this scenario analysis because both pitolisant trials (Dauvilliers and Szakacs) allowed concomitant therapy (i.e. removing these trials from the network would completely remove pitolisant from the comparison).

3.5.2 Discontinuation due to adverse events

The results of the company's NMA of discontinuation due to adverse events (presented in CS Appendix D Table 46) supports their economic model assumption that rates of discontinuation during the treatment initiation phase are equivalent for all treatments (see Section 4.2.6 of this ERG report). The results of the NMA of rates of discontinuation due to adverse events were low and there were no significant differences between treatments (CrI crossed zero for all relative treatment effects using both fixed effect and random effects).

3.6 Additional work on clinical effectiveness undertaken by the ERG

The ERG has updated the company's ITC to include additional relevant trial evidence, and to correct for data input errors, to inform the ERG's base case economic model.

3.6.1 Inclusion of additional arms and an additional study in NMA networks

As we stated in section 3.3.2, we consider that the unpublished Harmony Ibis trial (pitolisant versus modafinil and placebo) would meet the inclusion criteria for the ITC. We also believe that the 100-400 mg once daily modafinil arms of the Dauvilliers 2013 and Harmony Ibis trials should be included in the evidence network (but we agree with the company that the modafinil dose arm 200-600 mg from the trial by Black should not be pooled with the 100-400 mg doses). Therefore, we added the Harmony Ibis trial, including its modafinil arm, and the modafinil arm from the Dauvilliers trial to the ESS 8-weeks evidence network for the NMA that informs the ERG's base case economic model (Figure 3). We also conducted a scenario analysis in which the pitolisant dose used in the Harmony Ibis trial (<20 mg) was not pooled with pitolisant doses used in the Dauvilliers and Szakacs trials (<40 mg) (this scenario analysis is reported in Appendix 8).

This strengthened network connectivity and allowed an assessment of consistency in the placebo-pitolisant-modafinil closed loop. Furthermore, we identified that there were no serious TEAEs reported in the Szakacs RCT and hence this study should not be included in the serious TEAEs network. The ERG's network of evidence for serious TEAEs is shown in Figure 4. The network for discontinuations due to TEAEs has the same structure as the company's (CS Appendix D Figure 9).

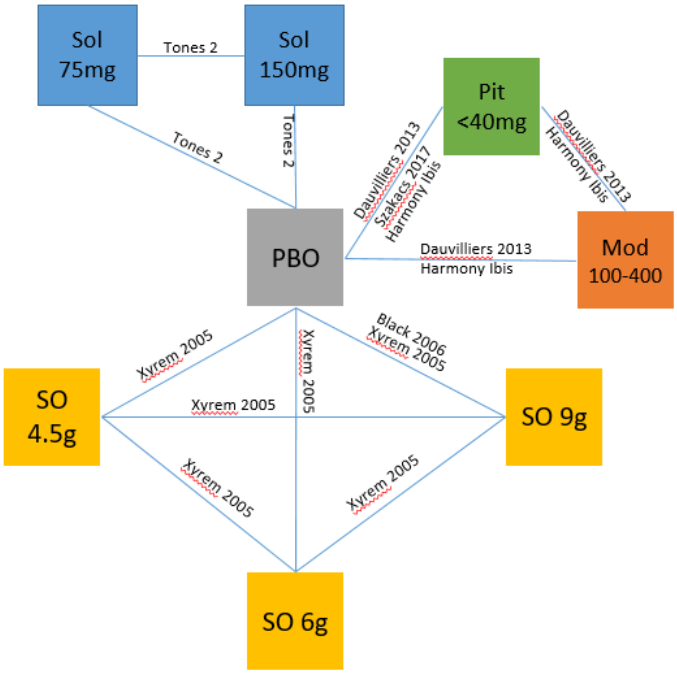

Figure 3 ERG's ESS week-8 network including modafinil and the Harmony Ibis trial

Abbreviations: Mod – modafinil; PBO – placebo; Pit – pitolisant; SO – sodium oxybate; Sol - solriamfetol

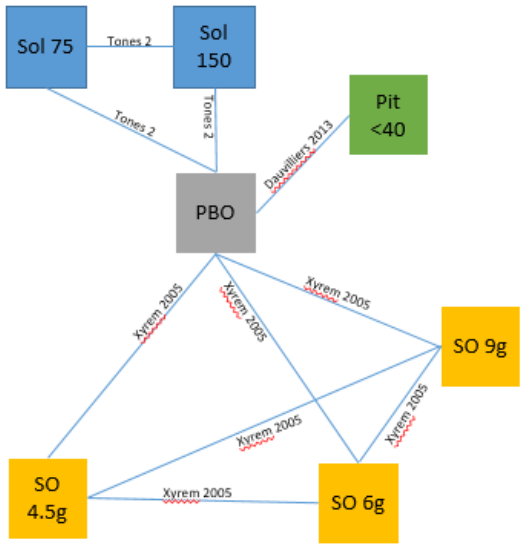

Figure 4 ERG's Serious TEAE network

Abbreviations: PBO – placebo; Pit – pitolisant; SO – sodium oxybate; Sol - solriamfetol

3.6.2 Corrections to input data and methods for imputing missing data

As described elsewhere in this report (Section 3.4.1 and Appendix 5) the ERG identified several errors and inconsistencies in the data extracted by the company and used in their NMAs of ESS 8-weeks, serious TEAEs and discontinuations due to TEAEs. We therefore

corrected the data extractions before conducting our analyses. Our input data are provided in Appendix 6.

3.6.3 NMA methods

For the NMA of ESS at 8-weeks (continuous outcome) we conducted a Bayesian NMA using the code as described in NICE DSU Technical Support Document 2.[41] WinBUGS (v.1.4) software was used to run this ITC.

Model fit, estimated using the DIC, for the fixed-effect model was 51.952 and for the random effects model was 52.274. Given the non-meaningful difference in the DIC we prefer to use the results of the random effects model because there is some clinical heterogeneity between studies.

For the NMAs of dichotomous outcomes (discontinuations due to adverse events and incidence of serious adverse events) we used MetaInsight software,[43] which we regard as providing more stable results, with narrower confidence intervals, when there are multiple zero events (i.e. AEs). Our results are expressed as relative risks (whereas the company reported risk differences).

3.6.4 Results of the ERG's additional analyses

Having corrected data input errors and including the Harmony Ibis trial, as well as including the modafinil arms from the Harmony Ibis and Dauvilliers studies, the results of the ERG's analysis (Table 20) are very similar to the results presented by the company. The results from an additional ESS scenario with separate pitolisant doses are presented in Appendix 8 but the ERG was not able to include this in health economic modelling due to the structure of the company's model.

Table 20 ESS week 8 and week 12 relative effects (as mean difference)

Relative effects of solriamfetol 150 mg compared to treatment	Fixed Effects		Random Effects	
	Mean	95% CrI	Mean	95% CrI
ESS 8 week (ERG base case)				
Placebo	-3.098	-4.865, -1.332	-3.098	-6.907, 0.707
Solriamfetol 75 mg	-1.8	-3.577, -0.024	-1.796	-5.615, 2.019
Pitolisant ≤40 mg	-0.581	-2.681, 1.52	-0.714	-5.224, 3.671
Sodium Oxybate 4.5 g	-2.968	-5.508, -0.423	-2.969	-8.245, 2.298

Relative effects of solriamfetol 150 mg compared to treatment	Fixed Effects		Random Effects	
	Mean	95% CrI	Mean	95% CrI
Sodium Oxybate 6 g	-1.968	-4.509, 0.573	-1.964	-7.248, 3.306
Sodium Oxybate 9 g	0.652	-1.582,2.889	0.654	-4.048, 5.353
ESS 12 week (ERG scenario)[a]				
Placebo	-3.798	-5.621, -1.976	-3.796	-7.589, 0.028
Solriamfetol 75 mg	-1.6	-3.448, 0.246	-1.597	-5.432, 2.232
Pitolisant ≤40 mg	-1.281	-3.428, 0.868	-1.414	-5.921, 2.987
Sodium Oxybate 4.5 g	-3.667	-6.26, -1.07	-3.676	-8.951, 1.596
Sodium Oxybate 6 g	-2.667	-5.261, -0.072	-2.67	-7.949, 2.597
Sodium Oxybate 9 g	-0.047	-2.334, 2.243	-0.05	-4.762, 4.645

Abbreviations: CrI, credible interval; ESS, Epworth Sleepiness Scale; SD, standard deviation.
A negative relative treatment effect represents an improvement (reduction) in ESS for solriamfetol 150 mg relative to the comparator.
[a] In this scenario 12 week data for TONES 2 was used in the network instead of 8-week TONES 2 data. The input data for the comparators remained the same as for the base case 8-week network.

The ERG's NMA of discontinuations due to TEAEs shows that, in comparison to placebo and with random-effects, sodium oxybate 9 g is associated with significantly higher risk of discontinuations. The results, expressed in terms of effects relative to solriamfetol 150 mg, (Table 21) indicate no significant difference in discontinuations due to TEAEs with any of the comparators under both the fixed-effect and random effects models.

Table 21 Discontinuations due to TEAEs (as relative risk)

Relative effects of solriamfetol 150 mg compared to treatment	**Fixed Effects**		**Random Effects**	
	RR	**95% CrI**	**RR**	**95% CrI**
Placebo	3	0.32, 28.02	3	0.26, 34.17
Solriamfetol 75 mg	3	0.32, 28.02	3	0.26, 34.17
Pitolisant ≤40 mg	4.38	0.19, 99.4	4.35	0.15, 122.43
Sodium Oxybate 4.5 g	6.25	0.23, 169.74	5.97	0.17, 210.41
Sodium Oxybate 6 g	1.45	0.09, 24.56	1.38	0.06, 31.67
Sodium Oxybate 9 g	0.35	0.02, 5.02	0.35	0.02, 6.51

The incidence of serious TEAEs in all the studies included in the ERG's NMA of serious TEAEs was low and the results expressed in terms of effects relative to solriamfetol 150 mg (Table 22) indicate no significant difference in serious TEAEs with any of the comparators under both the fixed-effect and random-effects models.

Table 22 Incidence of serious TEAEs (as relative risk)

Relative effects of solriamfetol 150 mg compared to treatment	Fixed Effects		Random Effects	
	RR	95% CrI	RR	95% CrI
Placebo	3.00	0.12, 72.18	3.00	0.12, 72.18
Solriamfetol 75 mg	3.00	0.12, 72.18	3.00	0.12, 72.18
Pitolisant ≤40 mg	3.10	0.08, 125.65	3.10	0.08, 125.65
Sodium Oxybate 4.5 g	1.13	0.01, 101.72	1.13	0.01, 101.72
Sodium Oxybate 6 g	1.05	0.01, 94.31	1.05	0.01, 94.31
Sodium Oxybate 9 g	0.92	0.01, 82.44	0.92	0.01, 82.44

3.7 Conclusions of the clinical effectiveness section

The company's decision problem is appropriate, and in particular, the ERG agrees that it is appropriate for the company to have restricted their population to adults with narcolepsy and EDS who have failed, or who are intolerant to modafinil, or for whom modafinil is contraindicated. The clinical experts who advised the ERG supports the positioning of solriamfetol for use as a second-line treatment option.

The ERG believes that the company has identified all the RCTs of solriamfetol after performing a search for clinical evidence that reflected their decision problem. Two placebo-controlled RCTs (TONES 2 and TONES 1) and one open-label study with a 2-week randomised withdrawal component (TONES 5) were identified and included. Of these, the TONES 2 is the pivotal phase III RCT and provides the key clinical effectiveness evidence. TONES 1 (phase IIb) provides supporting information on efficacy and safety of limited utility because patients only received a licensed dose of solriamfetol (150 mg) for 4 weeks. TONES 5 provides open-label data on efficacy (for patients on 75 mg, 150 mg or 300 mg solriamfetol) and safety for up to 52 weeks and randomised evidence on the effects of the withdrawal of solriamfetol. None of the trials enrolled any patients from the UK.

TONES 2 was a multicentre 12-week, four-arm RCT comparing three doses of solriamfetol (75 mg, 150 mg or 300 mg once daily) against placebo (safety population n=236, [redacted] in each arm). The 300 mg solriamfetol dose is not licenced and so is not considered in the CS or this ERG report. The trial was of good methodological quality and judged to be at a low risk of bias. The trial enrolled people with narcolepsy both with and without cataplexy. Clinical advice to the ERG was that, based on the information available, the TONES 2 population was similar to the established population of people with narcolepsy in the UK.

The co-primary efficacy outcomes for TONES 2 were the change in ESS from baseline to week 12 and the change in MWT40 from baseline to week 12. The mean improvement in ESS score at week 12 for participants in the solriamfetol 75 mg and 150 mg arms compared to baseline were clinically significant (LS mean change solriamfetol 75 mg -3.8, SE 0.7; 150 mg -5.4 SE 0.7, placebo -1.6 SE 0.7). The mean differences relative to placebo were statistically significant for both solriamfetol arms [Mean difference (95% CI) solriamfetol 75 mg -2.2 (-4.0 to -0.3), p=0.0211; solriamfetol 150 mg -3.8 (-5.6 to -2.0), p<0.0001). For the MWT40, a statistically significant improvement relative to placebo was observed for the solriamfetol 150 mg dose at week 12 (p<0.0001) but not for the 75 mg dose (p=0.1595).

The company's designated key secondary outcome of the proportion of patients who reported improvement in PGI-c score at 12 weeks showed that there were dose-dependent increases in the proportions of patients in receipt of solriamfetol who reported improvement which were significant for the solriamfetol 150 mg dose compared with placebo (78.2% versus 39.7% respectively, p<0.0001). The comparison of the 75 mg solriamfetol dose with placebo was below the hierarchical break in the fixed hierarchical testing approach used to account for multiplicity.

HRQoL was measured using both generic tools (SF-36v2, EQ-5D-5L Index and EQ-VAS) and a disease-specific tool (FOSQ-10) from baseline to week 12.

[redacted].

Efficacy results from TONES 1 after 4-weeks treatment with solriamfetol 150 mg were consistent with those from TONES 2. The open label phase of TONES 5 showed that improvements in ESS could be maintained for up to 52 weeks.

The most frequently reported adverse event was headache in all three TONES studies and the

[redacted].

There were no head-to-head comparisons of solriamfetol against any of the comparators listed in the NICE scope so the company carried out 12 NMAs to indirectly estimate ESS and nine other outcomes for solriamfetol relative to comparators where data was available. Although 7 RCTs met the inclusion criteria for the indirect comparison not every study was included in every NMA. We identified one pitolisant RCT that we believed had been

excluded inappropriately. No evidence that could be used in an indirect comparison was identified for the comparators dexamphetamine or methyphenidate.

The only NMA used to directly inform data inputs to the company's base case economic model is the ESS change from baseline at 8 weeks. The company favoured the fixed-effect model which shows solriamfetol 150 mg provides an improvement in ESS relative to placebo, solriamfetol 75 mg and sodium oxybate at a dose of 4.5 g. Credible intervals for comparisons with sodium oxybate 6 g, sodium oxybate 9 g and pitolisant ≤40 mg all cross zero. Due to between-study heterogeneity, the ERG favours the random-effects model where credible intervals cross zero for every comparison. The NMAs for discontinuation due to adverse events supported the company's assumption in the economic model that rates of treatment discontinuation during the initiation phase is equivalent for all treatments.

The ERG has added a pitolisant RCT (Harmony Ibis), including its modafinil treatment arm and a modafinil treatment arm from another RCT (Dauvilliers) already included to the network meta-analysis. We have corrected errors and inconsistencies in the input data, which also resulted in the loss of one study (Szakacs) from the serious TEAEs network because no serious TEAEs were reported for this study. Our results for ESS at 8-weeks are very similar to the results presented by the company. When comparing the relative effects of solriamfetol 150 mg to other treatments from the random effects model (which is the ERG's preferred choice) the 95% credible intervals cross zero in every case. For the ERG's NMA of discontinuations due to TEAEs the effects relative to solriamfetol 150 mg indicate no significant difference in comparison to any of the comparators under both the fixed-effect and random-effects models. A similar finding was obtained in the ERG's NMA of incidence of serious TEAEs where the confidence intervals around the relative risk for each comparator were very wide.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review of economic evaluations for narcolepsy (CS section B.3.1). Since no NICE technology appraisals for narcolepsy were found, the company performed an ad-hoc search to identify technology appraisals for obstructive sleep apnoea (OSA). One NICE HTA, TA139 was identified.[4] This, and another UK-specific cost-effectiveness study from the systematic review (Lanting et al. 2014[44]) were used to inform the company's analysis (see CS Table 37). We summarise key issues in Table 23 below.

Table 23 Features of UK economic analyses that informed the company analysis

Feature of model	**TA139[4,45]**	**Lanting et al. 2014[44]**
Population	Adults with OSAHS	Narcolepsy with cataplexy
Treatment	CPAP devices	Standard treatment plus sodium oxybate
Comparators	Dental devices and lifestyle management	Standard treatment alone
Model	Markov model including utility effect of OSAHS and disutility and mortality associated with effects on incidence of CHD and stroke (via SBP) and RTAs (via ESS).	Markov model with 3 health states: *On Treatment*, *Withdrawn from Treatment* and *Dead.* Treatment response was assessed at 3 months and patients with AEs or non-response stopped treatment.
Time horizon	Lifetime	5 years
Cycle length	1 year	3 months
Change in ESS due to treatment discontinuation	Patients stopping treatment were assumed to return immediately to levels of ESS, SBP and utility associated with no treatment.	Not reported
Treatment discontinuation rate	The percentage of patients compliant at 2 and 3 years after treatment initiation (74% and 73%) were used to model the rate of discontinuation from years 1 to 4.	During the first 3 months, non-responders (75%) and patients with AEs (3.4%) withdrew from sodium oxybate and continued standard treatment alone. No withdrawal is assumed after the first 3 months (due to the lack of evidence).

Feature of model	**TA139[4,45]**	**Lanting et al. 2014[44]**
Utilities	Linear regression model to predict utility (EQ-5D or SF-6D) from ESS, controlling for baseline utility and ESS ('McDaid algorithm').[45] Utility loss due to CHD, stroke and RTAs from literature.[46]	Baseline utility estimated by mapping SF-36 results from Teixeira et al. 2004 to EQ-5D.[47,48] McDaid algorithm used to relate changes in ESS to changes in utility.[45]
Costs	The initial costs of the interventions and the ongoing costs of care associated with the interventions, including doctor appointments and any healthcare use due to stroke, CHD and RTAs.	The costs of sodium oxybate (average daily dose of 6 g) and the standard treatments of stimulants (modafinil, dexamfetamine and methylphenidate) and antidepressants (clomipramine, fluoxetine and venlafaxine), and the cost of consultant outpatient clinic attendance; no additional costs associated with AEs for either treatment.
Discount for costs and utilities	3.5%	3.5%
Perspective	NHS and PSS	NHS

Abbreviations: *AEs adverse events, CHD coronary heart disease; CPAP continuous positive airway pressure, ESS Epworth Sleepiness Scale, OSAHS obstructive sleep apnoea/hypopnoea syndrome, PSS Personal Social Services; RTA road traffic accident; SBP systolic blood pressure*

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

See Table 24 for the ERG assessment of whether the company's submitted economic evaluation meets NICE Reference Case requirements. We have concerns about the method of utility estimation, as the company's mapping approach introduces uncertainty. However, on balance we conclude that it is better than available alternatives (see section 4.2.7 below).

Table 24 NICE reference case checklist

Element of HTA	Reference case	ERG comments on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, patients only
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, lifetime with sensitivity analysis for shorter periods
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. QALYs with utilities from mapping of ESS to EQ-5D-5L
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes. EQ-5D-5L completed by NHSW online sample with self-reported OSA and/or narcolepsy
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Not clear. NHWS EQ-5D-5L utilities valued by van Hout cross-walk but not specified if UK value set is used
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Abbreviations: *PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome; NHWS National Health and Wellness Survey 2016*

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company's model is described in CS section B.3.2.2. It is comprised of a decision tree for the treatment initiation period (Figure 5), followed by a Markov model (Figure 6).

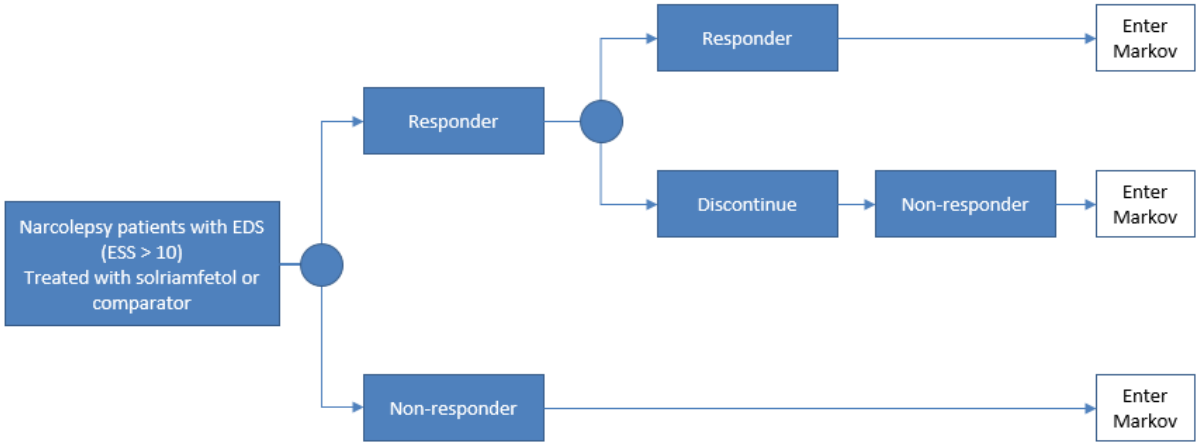

Figure 5 Treatment initiation – Decision tree

Source: reproduced from CS Figure 14

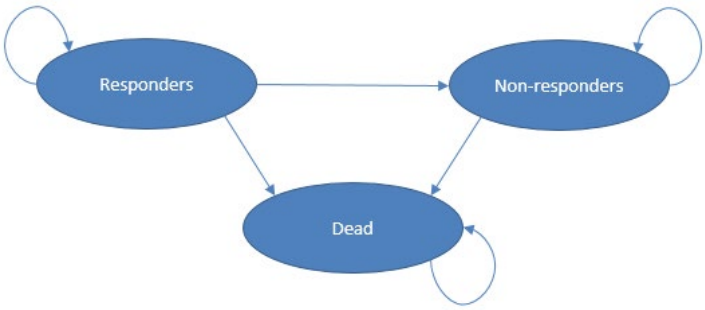

Figure 6 Maintenance treatment – Markov model

Source: reproduced from CS Figure 15

A cohort of patients enters the decision tree model with an initial ESS score ([redacted] in the base case) at the start of treatment with solriamfetol or one of the comparators. At a defined time (8 weeks in the base case) patients are assessed and classified as: *responders (*reduction of 3 points or more in ESS from baseline) or *non-responders*. In addition, patients who withdraw from treatment during the initiation period because of an adverse event are classified as non-responders.

The Markov model (Figure 6) consists of three mutually exclusive health states: *Responder, Non-responder* and *Dead*. The model has a yearly model cycle, with a half-cycle correction.

Patients who enter the Markov model in the *Responder* health state stay there and continue treatment until they lose response, stop treatment because of an adverse event or die. Patients in the *Responder* state are assumed to have the same treatment-specific ESS score for the duration of the analysis. When patients enter the *Non-responder* health state, they are assumed to stop treatment and their ESS score immediately returns to the baseline value. No further lines of therapy are modelled and non-responders remain in the *Non-responder* health state until death.

The main clinical outcomes that drive the economic model are the mean change from baseline ESS, estimated from the ITC analysis (see section 3.5 above). These results are used in two ways: to estimate the proportion of responders to each treatment (CS B.3.3.1); and to estimate the mean ESS for responders and for non-responders (CS B.3.3.2). Health state utilities are then calculated as a function of ESS and other cohort characteristics (CS B.3.4.3). Table 25 below shows the estimated proportions of responders and the mean ESS and utilities for responders and non-responders in the company's base case analysis (as reported in CS Tables 41 and 43). We discuss the estimation of these parameters in sections 4.2.6 and 4.2.7 below.

Table 25 Base case estimates of response, mean ESS and utility

Drug	*Daily dose*	*Respon-ders*	*Mean ESS*		*Mean utility up to week 8* [a]	
			Responders	*Non-responders*	*Respon-ders*	*Non-responders*
Solriamfetol	75 mg	50%	10.22	17.73	0.682	0.591
	150 mg	65%	9.58	16.72	0.683	0.605
Pitolisant	≤40 mg	65%	9.53	16.67	0.683	0.605
Sodium oxybate	4.5 g	33%	10.15	18.05	0.682	0.587
	6 g	50%	10.37	17.86	0.681	0.590
	9 g	65%	8.92	16.07	0.685	0.613

Source: Adapted from CS Tables 41 and 43

[a] Utility is adjusted for age. Values shown here for initial cohort age of [redacted] years.

The company argued that an alternative model structure with categorisation by level of ESS score (no EDS, mild, moderate or severe EDS as outlined in the NICE Clinical Knowledge Summary[49]) was inappropriate: primarily because UK clinicians rarely use such a categorisation (CS page 144). Our experts confirmed this.

The ERG considers the model structure to be reasonable. We discuss specific issues relating to the model assumptions and parameter estimates below.

4.2.2.2 ERG critique of model assumptions

4.2.2.2.1 Definition of response

The company use ESS as the measure of EDS in the economic model (B.3.3). This was justified on several grounds. Firstly, ESS was a co-primary endpoint in the TONES 2 and TONES 5 studies. Secondly, it was the most commonly reported efficacy outcome across comparator RCTs identified by the clinical effectiveness systematic review and used in the ITC. And finally, it was the primary measure of EDS used in the UK economic analysis for sodium oxybate for narcolepsy (Lanting et al. 2014[44]) and the analysis of CPAP in OSA for TA139.[4] Another efficacy outcome, Maintenance of Wakefulness Test (MWT), was considered but is not used in the model because, as the company argue, it is not widely used in clinical practice beyond initial diagnosis. Our experts concur with this statement.

In the model, treatment response is defined by a reduction of 3 or more points from baseline ESS, irrespective of the absolute baseline value. The same approach was used in the McDaid et al.[45] analysis for TA139 and by Lanting et al.[4,44] The company state that according to the results of the KOL Clinical Practice Interviews, subjective reports of improvement in symptoms (such as ESS) are important clinical outcomes in managing EDS due to narcolepsy. We note, however, that some experts who participated in the interviews suggested that it would be unreasonable to consider the change in ESS alone when assessing treatment response, and that it is rather normalisation in the ESS score that is most important. Experts consulted by the ERG agreed that they would not base treatment decisions purely on change from baseline ESS.

4.2.2.2.2 Timing of ESS change and response assessment

The improvement in ESS and the associated impact on utility is assumed to occur one week after treatment initiation for all therapies. The company state that this reflects observed outcomes from TONES 2 for solriamfetol (CS Figure 4) and the fact that the first post-baseline measurements in comparator trials were taken at 2, 4 or 7 weeks, which does not allow assessment of the relative timing of onset for treatment effects. Expert advice to the ERG is that this approach is reasonable.

The company assumed that response would be assessed at 8 weeks in the base case analysis. They explained this choice by the absence of established timing of clinical assessment and the availability of comparator data for use in the ITC, which were limited to a maximum of 8 weeks (see section 3.3.2 above). The company also report results for 12-week assessment in a scenario analysis. Expert advice to the ERG is that change in ESS is

likely to be similar at different time points (4, 8 and 12 weeks), except for sodium oxybate which can take up to 12 weeks in patients with EDS.[50] As sodium oxybate trials used in the ITC were conducted for no more than 8 weeks, the efficacy of this treatment is likely to be underestimated.

4.2.2.2.3 Treatment discontinuation

The SmPC states that "*the need for continued treatment and the appropriate dose should be periodically assessed during extended treatment in patients prescribed solriamfetol*".[3] The model does not include an explicit reassessment of response (a 'stopping rule'), but it does assume that a proportion of patients will stop treatment in the initiation phase and in ongoing maintenance treatment due to loss of response or adverse events (CS section B.3.3.4 and B.3.3.5 and section 4.2.6.2 below).

The company assumed that ESS returns to the mean baseline value immediately after treatment discontinuation. They justified this based on the results from the two-week randomised-withdrawal phase of TONES 5 (where patients experienced increased EDS within 2 weeks of treatment discontinuation, with the mean ESS trending towards baseline), and the half-life for solriamfetol and the comparators (under 12 hours for all treatments). The company did not conduct any sensitivity analyses over waning of treatment effects after discontinuation, although the model does include two alternative assumptions: change of ESS persists for model duration; and non-responders see no change in ESS.

4.2.2.2.4 Changes during ongoing treatment

In the model, dose is assumed constant for solriamfetol and comparators while patients continue on treatment. We note that over a year of follow up in TONES 5, [redacted] (CS TONES 5 CSR). We note that there is wider uncertainty over the dose mix for solriamfetol and comparators that would be likely to be used in routine UK clinical practice, which we explore in ERG scenario analysis (see section 6 below).

The mean ESS for responders is also assumed to remain constant thoughout the time horizon. The same assumption was made in previous economic evaluations (Lanting et al. 2014[44] and TA139[4]). With regard to change over time in the symptoms and severity of

narcolepsy (reflected in the model through non-responder ESS and related utility), the company state:

> "*Based on KOL Clinical Practice Interviews, there was limited clinical opinion that suggested a slight improvement in ESS may occur in some patients, over decades, later in life; however this was generally felt to only be due to adaptation and lifestyle adjustment by the patient, and only reflected in small improvement in ESS, for example around 1 ESS point. We are unaware of any published evidence that supports that there is a change in ESS associated with narcolepsy over time since diagnosis, or due to aging. Furthermore, in contrast, some clinicians also felt that there was no such improvement over time*." (Clarification Response B3)

Given the lack of information about changes in narcolepsy symptoms or treatment effectiveness over time, with or without solriamfetol or comparator treatments, it is reasonable to assume no change in ESS or related utility through the model time horizon.

4.2.2.2.5 Impact of adverse effects

As noted above, the model includes discontinuation, and hence loss of efficacy and associated utility, due to adverse events. Otherwise, the model does not include any utility loss or cost associated with adverse events (CS B.3.3.3). The company justify this on the basis that most adverse events occur early in the course of treatment, are self-limiting and resolve quickly. This approach is reasonable. It is very unlikely that the model would be sensitive to the direct impact of adverse effects on cost and health outcomes. The absolute incidence of serious adverse events is low and estimates of relative risks from our ITC are very uncertain.

4.2.2.2.6 Assumptions about mortality

The company assume that the treatments considered in the submission have no effect on patients' survival. Therefore, mortality is estimated from general population life tables,[51] adjusted for narcolepsy by applying 1.43-fold excess mortality in female patients and 1.57 in male patients (following Ohayon et al. 2014[52]), and is the same in all arms. We agree with this approach.

4.2.2.2.7 Ommission of other potential impacts

Road traffic accidents: The company states (CS page 145) that there is an association between EDS and increased risk of road traffic accidents.[53] This was modelled in TA139.[4] However, in the UK narcolepsy is a 'notifiable' medical condition (i.e. people with uncontrolled EDS must surrender their driving licence). In TONES 5, [redacted](TONES 5 CSR page 47). We agree that the risk of solriamfetol or comparators affecting the risk of traffic accidents is negligible, so it is reasonable that this risk has been omitted from the economic model.

Cardiovascular events: In TA139,[4] the mortality and morbidity associated with coronary heart disease and strokes were incorporated by modelling treatment-associated changes in systolic blood pressure (see Table 23). We note that the SmPC states that solriamfetol "*increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose dependent fashion*". [3] The company argue that the impact of solriamfetol on systolic blood pressure in the pivotal trial was minimal, and therefore have not modelled the risks of cardiovascular events (CS section B.3.2 page 146). We agree.

ERG conclusions:

- We consider the model structure appropriate for the decision problem.
- In the company's economic model, reduction in ESS scores from baseline is used as the measure of treatment response. However, clinical experts say they would not use change in ESS alone to identify treatment responders without consideration of other factors, such as impact of treatment on quality of life.
- There is uncertainty over the timing of response assessment. We think that the company's argument for using the 8-week time point in the base case is reasonable. We considered whether a 12-week assessment would be better: because this was the primary end point in TONES 2 and clinical advice is that, although change in ESS is likely to be similar at 4, 8 and 12 weeks for most comparators, sodium oxybate can take about 3 months before an improvement is seen. However, using 12 weeks would introduce inconsistency with data from comparator trials (which was available for a maximum of 8 weeks).
- The model includes a number of simplifying assumptions related to the lack of long-term data on narcolepsy outcomes and persistence of treatment effects. These include assumptions that after the initial treatment period, medication doses do not change; that mean ESS for both responders and for non-

responders does not change as patients age; and that treatments do not affect survival.

- In addition, the model does not include further lines of therapy after discontinuation of the second-line treatments, which does not reflect UK clinical practice where non-responders usually "cycle" through different treatments for EDS during their lifetime.
- The effect of treatment on the risks of cardiovascular events and stroke is not modelled since the change in systolic blood pressure in the TONES 2 trial was minimal. Our clinical experts confirmed this. We note that excluding the effect of CPAP on cardiovascular events from the analysis in TA139[4] did not lead to significant changes in the cost-effectiveness results.
- We agree that these simplifications are unavoidable but note that they are associated with structural uncertainty that is not reflected in the probabilistic or deterministic sensitivity and scenario analysis.

4.2.3 Population

The company restricts the decision problem to people for whom modafinil has failed or who cannot take modafinil due to intolerance or contraindication. See section 2.3 above for discussion of the ERG view on the company's decision problem.

The modelled population are patients with EDS due to narcolepsy, where EDS is defined as ESS score >10. We note that there is only one patient in the IPD dataset for solriamfetol 150 mg arm (which is used to estimate response rates) who did not satisfy this criterion and had ESS = 10 at baseline. The clinical advice to the company suggests that this threshold may vary in clinical practice and ESS < 12 may also be considered as successful treatment. The company did not model any alternative thresholds in their sensitivity analysis. We conducted an exploratory analysis with this threshold, but this had no effect on the results. Therefore, we do not explore the uncertainty in this parameter further.

Baseline characteristics of the modelled cohort are based on the solriamfetol 150 mg mITT population of TONES 2 (see Table 26). In Clarification Response B1, the company explain that their decision to base the cohort on this arm, rather than the whole randomised population, was because the model uses the individual patient data for this arm of the trial (see section 4.2.6 below for further details on their approach).

Table 26. Baseline characteristics for the modelled cohort

Baseline characteristic	Value used in the base case	
	Company[a]	ERG[b]
Age, years	[redacted]	[redacted]
Female, %	[redacted]	[redacted]
ESS score at baseline	[redacted]	[redacted]

Source: adapted from CS Table 7 and CS Table 38 Abbreviations: ESS, Epworth Sleepiness Scale; mITT, modified intent to treat; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness
[a] Based on the baseline characteristics for solriamfetol 150 mg mITT population [redacted]
[b] Based on the baseline characteristics of patients recruited to TONES 2 except 3 patients who did not receive treatment (n = 236)
Note: Data are presented as mean (SD) unless otherwise stated.

The NICE scope does not request any subgroup analyses. However, the CS does present cost-effectiveness results for the subgroup of TONES 2 patients who had previously been treated with modafinil (CS section B.3.9.1). We consider this to be useful, as it reflects the company's decision problem. However, the subgroup analysis is subject to uncertainty because it is based on individual patient data for a small number of patients ([redacted] patients in the TONES 2 150 mg arm).

Presence or absence of cataplexy was a pre-defined subgroup in TONES 2 (section 3.2.5.3 above). However, the company state that as there is no evidence to suggest that solriamfetol would impact cataplexy it was not assessed in the cost-effectiveness analysis (Clarification Response 2). This is reasonable.

ERG conclusions:

- The company use baseline characteristics of the solriamfetol 150 mg mITT population of TONES 2 for the model cohort. We believe that the cohort should represent the whole eligible population recruited to the pivotal trial, regardless of to which treatment they were allocated (n = 236). We make this change in the ERG analysis, although it makes little difference to the overall results.
- There is uncertainty over whether the TONES 2 population (or those randomised to the 150 mg solriamfetol dose) is representative of the UK population.

The CS presents cost-effectiveness results for the subgroup with prior modafinil use, which reflects the company's target population. However, this is subject to uncertainty because it is based on individual patient data for a small number of people.

4.2.4 Interventions and comparators

The intervention of interest is solriamfetol (Sunosi®, Jazz Pharmaceuticals). According to the SmPC for solriamfetol,[3] "*the recommended starting dose is 75 mg once daily. If clinically indicated in patients with more severe levels of sleepiness, a starting dose of 150 mg may be considered. Depending on clinical response, the 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 once daily.*"

In the base case, the company present cost-effectiveness results separately for 75 mg and 150 mg doses as well as combined results assuming an equal split of the two doses. The assumed dose mix is based on the current usage of this drug in the US (CS B.3.5.1). The company consider scenarios with alternative assumptions of 70% / 30 % and 30% / 70% for the 75 mg and 150 mg doses. The dose mix that would be used in the UK is unknown. The company argue that the mix in the TONES 5 study is not necessarily reflective of how it would be used in clinical practice, because [redacted] (CS TONES 5 CSR).

The comparators included in the company's base case are pitolisant and sodium oxybate (4.5 g, 6 g and 9 g doses), while dexamfetamine and methylphenidate are only considered in scenario analyses as they could not be included in the ITC due to the lack of robust clinical evidence (see section 3.3.2). Base case results for sodium oxybate 4.5 g, 6 g and 9 g doses are presented in the same manner as those for solriamfetol: i.e. separately for each individual dose as well as combined assuming an equal split. A clinical expert consulted by the ERG suggested that this is a reasonable assumption, although there is no evidence that it reflects how pitolisant is used in UK practice.

Modafinil was specified as a comparator in the NICE scope but is not included in the economic evaluation because it is the established first-line therapy for managing EDS in patients with narcolepsy and so falls outside the company's defined decision problem.

The comparator treatments are further described in Appendix 9.

ERG conclusions:

- Evidence on the uptake of different doses of solriamfetol in UK clinical practice is limited. However, based on clinical advice, we consider that assuming a higher than 50% market share for solriamfetol 150 mg in the main analysis would be more reasonable.
- The ERG concur with the company's decision to exclude modafinil from consideration as a comparator on the basis that it is the established first-line therapy for managing EDS in patients with narcolepsy in the NHS.

Dexamfetamine and methylphenidate are excluded from the company's base case due to limited clinical evidence. We have been advised by our clinical experts that there is a wide variation with respect to using these medications in patients with narcolepsy in the UK. The company state in their submission that dexamfetamine and methylphenidate comprise only 17.4% and 2.7% of the narcolepsy market, respectively, and the use of these drugs has been declining. Our experts consider these estimates reasonable.

4.2.5 Perspective, time horizon and discounting

In the company's economic analysis, only the direct health effects of treatments are modelled and costs are estimated from the perspective of the NHS and Personal Social Services (PSS). Costs and outcomes are discounted at 3.5% in the base case, and 0% and 6% discounts are applied in sensitivity analyses.

In the base case, costs and QALYs are estimated over a lifetime time horizon. The cost-effectiveness results for alternative time horizons within the range of 5 to 70 years, considered in scenario analyses do not change the overall outcomes. This is explained by the fixed cost of treatment per year, the assumption of equal survival for all treatment arms and equal utilities for all non-responders, who quite quickly predominate due to discontinuation rates (see Markov traces in CS Appendix J.1.1).

ERG conclusions:

- Narcolepsy is a chronic condition. Therefore, given the NICE guidelines, a lifetime time horizon adopted by the company in their base case is appropriate. Although there is uncertainty over long term outcomes, a shorter time horizon does not alter the cost-effectiveness results.
- Discounts to both costs and outcomes are applied in line with the NICE guidance.

4.2.6 Treatment effectiveness

4.2.6.1 ESS and response

The company describe the method that they use to estimate the proportion of responders, and the mean ESS for responders and non-responders in CS section B.3.3.1 and B.3.3.2.

The model includes individual-level data for patients randomised to solriamfetol 150 mg in TONES 2 (n = 55). Of these patients, 54 met the definition of EDS as ESS > 10 at baseline (mean baseline ESS 17.1). Response is defined in the model as a reduction of 3 or more points in ESS from treatment initiation to 8 weeks (i.e. ΔESS ≥ 3). This criterion was met by 35 of the 54 patients with EDS (65%); and the mean ESS at week 8 was 9.58 for the responders and 16.72 for the non-responders. These results represent the base case estimates of treatment response for 150 mg solriamfetol (see Table 25 above).

For the other treatments (including solriamfetol 75 mg), the clinical results are estimated by generating a 'pseudo-IPD' dataset, illustrated in Figure 7 below. This involves adjusting the original IPD change from baseline (ΔESS) values by the relative effects (mean difference in ΔESS) from the ITC (CS Table 25). For example, the mean difference in ΔESS for sodium oxybate 4.5 g versus solriamfetol 150 mg in the company's ITC was -2.946. Adding this to the change from baseline ESS for each person in the IPD dataset "shifts" the distribution of ΔESS to the right (as in Figure 7). Each patient in the pseudo-IPD dataset is then classified as a responder or non-responder. Hence, the proportion of responders and the mean ESS can be calculated for each treatment arm. For sodium oxybate 4.5 g, this process results in an estimated response rate of 33% and mean ESS of 10.15 and 18.05 for responders and non-responders, respectively.

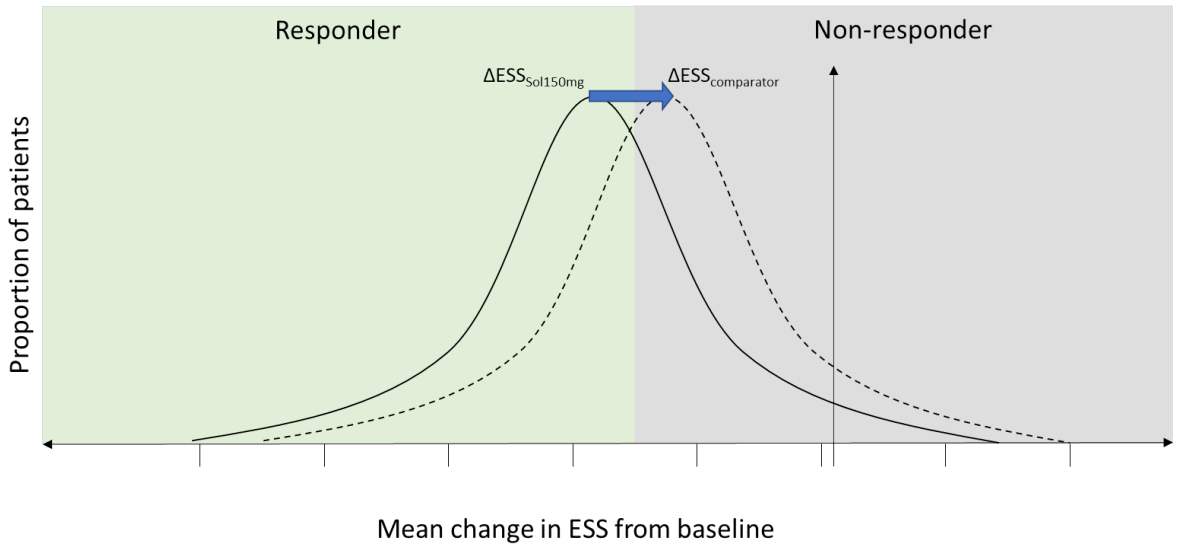

Figure 7 Transformation of IPD for comparator

Source: reproduced from CS Figure 17
Abbreviations: ESS Epworth Sleepiness Scale, IPD individual patient level data. Δ represents change in ESS from baseline. Solid line represents solriamfetol, dashed line represents transformed data for comparator. A responder is defined as a patient achieving a reduction in ESS ≥3.

The company state that the choice of the IPD for solriamfetol 150 mg as the reference point in the economic analysis was arbitrary (Clarification Response A25). On request from the ERG (Clarification Response A25), the company conducted a cost-effectiveness analysis with solriamfetol 75 mg as the reference arm. Results are similar to the base case.

In the company's model, the proportion of patients responding to the 150 mg dose of solriamfetol at week 8 is derived either directly from the IPD dataset (as explained above) or from a non-parametric bootstrap sample of the size 5,000 randomly drawn (with replacement) from the IPD (Gray et al. 2010[54]). Economic outcomes in the base case are presented for both bootstrapped (CS Tables 48 and 49) and raw IPD approaches (CS Tables 50 and 51). As might be expected, the results are very similar.

The company's probabilistic sensitivity analysis (PSA) is also based on bootstrapped samples of the size 5,000. As the company state in Clarification Response B8, the same sample size was used to allow for consistent point of reference. For each PSA iteration, the (treatment-specific) mean change from baseline relative to solriamfetol 150 mg is sampled using a normal distribution (with CI shown in CS Table 46 page 183), and this figure is applied to all bootstrapped pseudo-IPD patients generated within the PSA simulation (Clarification Response A24b). The company have acknowledged that this may artificially reduce uncertainty, and have re-run the PSA with a bootstrap sample size aligned with the

TONES 2 150 mg arm (n = 54) (see Clarification Response B8). The results are presented in Clarification Response Appendix A.

ERG conclusions:

- The company's approach to the estimation of treatment response and mean ESS for responders and non-responders is reasonable, given the lack of evidence for comparators based on the same definition of treatment response.
- The method relies on a small IPD dataset for one treatment arm: 54 patients randomised to solriamfetol 150 mg in TONES 2. This may bias results if the sample is not representative of UK patients with EDS due to narcolepsy. The method also assumes that the distributions of ESS change are similar for the different treatments, which may not be accurate if the mechanisms of action for the treatments differ substantially (see Table 44 in Appendix 9).[55]
- Deterministic results should be based on direct estimates from the original IPD dataset, not from a mean of bootstrapped samples.
- We do, however, consider it appropriate to use non-parametric bootstrapping in the probabilistic analysis. The histogram of ΔESS at week 8 for solriamfetol 150 mg IPD suggests that the distribution is non-normal and skewed to the left. The bootstrap can take account of patient-level heterogeneity without making assumptions about the form of the underlying distribution.
- However, the way in which bootstrapping was applied in the company's PSA will have underestimated uncertainty. A basic principle of the non-parametric bootstrap is that re-samples should be of the same size as the original dataset: to retain information about sampling variation. Thus, each PSA iteration should combine results from one non-parametric bootstrap sample of the same size as the original IPD (n = 54) with one set of random draws from the probability distributions for other model parameters. Inflating the bootstrap sample size to 5,000 per PSA iteration artificially reduces uncertainty. We also note that calculations at the individual level should also have allowed for variation in the treatment effect (rather than adding exactly the same mean difference to the ΔESS for each individual).

4.2.6.2 Treatment discontinuation

The company assume that the rate of discontinuation due to AEs during the 8-week treatment initiation phase is equivalent for all treatments, since the ITC did not demonstrate a statistically significant difference in the rates of discontinuation due to serious TEAEs (see CS Appendix D Table 42).

Since no long-term evidence was available on treatment discontinuation rates due to AEs, the modelled annual rate of discontinuation in the maintenance phase was estimated from TONES 5. In the open-label phase of this trial, 76 (33.6%) out of 226 patients with narcolepsy (all doses - 75, 150 and 300 mg - combined) did not complete the study, including 17.3% of patients who discontinued treatment due to the lack of efficacy and 10.2% due to AEs (TONES 5 CSR Table 5 page 76). Most AEs (56.8%) occurred within the first 4 weeks of treatment, and therefore, the rate of discontinuation due to AEs in the following weeks was estimated at 4.4% (which is 43.2% of 10.2%). This parameter value is used to model discontinuation in the maintenance phase. We note that in TONES 5, AEs were defined as those

[redacted]

during TONES 5, not the parent study (CS section B.2.10 page 112). The company argue that since the solriamfetol arm in TONES 5 included the unlicensed 300 mg dose, the modelled rate of discontinuation due to AEs is likely to be overestimated.

As mentioned above, treatment discontinuation due to loss of response was observed in 17.3% (39/226) participants with narcolepsy in TONES 5.[56] When estimating the discontinuation rate due to loss of response, the company assume that a proportion of these discontinuations would have occurred during the initiation phase (i.e. the decision tree component) because some of the patients in TONES 5 had a break in treatment before entering the study. The CS reads: "*TONES 2 showed that during 12 weeks of treatment, 6.4% (11/173 patients treated with solriamfetol) of patients discontinued due to loss of efficacy;*[17] *as such the current analysis assumed that 10.9% of patients (17.3% minus 6.4%) would discontinue due to loss of response within the first year*" (CS section B.3.3.5).

ERG conclusions:

- The company's arguments regarding treatment discontinuation due to AEs seem reasonable. Assuming the same discontinuation rate across all treatments (based on TONES 5) due to lack of long-term evidence is appropriate for the base case. The modelled rate, however, is likely to be an overestimate since the solriamfetol

arm in TONES 5 included the unlicensed 300 mg dose. A scenario analysis based on the results from the ITC for discontinuation due to serious TEAEs (see section CS Appendix D.1.5.6) would be useful.

- Similarly, discontinuation due to loss of response in the maintenance phase (based on the TONES trials) is assumed to be the same for all treatments, 10.9% per year. It is not possible to validate this estimate, as we do not have access to the relevant information from the pivotal trials. Clinical advice suggests that the discontinuation rate due to loss of response is slightly lower in clinical practice.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company report a systematic literature review to find utility values for people with EDS caused by narcolepsy (CS Appendix H). They identified seven studies, with utility values based on either the EQ-5D or SF-36.

- **EQ-5D based utilities** (Table 28): Four studies reported EQ-5D index scores for narcolepsy cohorts.[57-60] The cohorts were from single treatment centers in Germany, Italy and France and were restricted to adults (age 18 years and over) with mean ages from 37 to 49 years. It is unclear if the results are transferable to UK settings or general population preferences (EQ-5D-3L 'UK Tariff' scores).[61] Despite this, estimates are remarkably consistent between studies: 0.86-0.87, except at baseline for 41 patients with follow up in the Dauvillers study (0.83).

SF-36 based utilities (Table 29**):** Three studies reported utility estimates derived from the generic SF-36 heatlh outcome questionnaire.[44,62,63] The resulting utility estimates were lower than those obtained with the EQ-5D, with more variation between studies. Some of this variation is likely to have resulted from the use of different valuation methods in addition to differences between the populations. Flores et al. (2016) found significantly lower utility estimates for people with narcolepsy than for matched controls from US National Health and Wellbeing Survey (NHWS) data.[63] Bolin et al. (2017) reported higher utility scores in a cohort after treatment with sodium oxybate than before.[62]

This literature may be seen to support the company's argument that the EQ-5D is insensitive to the impact of narcolepsy on quality of life and that estimates are close to general population values (CS section B.3.4.1). For comparison, we show UK general population utilities from the EQ-5D-3L and SF-6D in Table 27. Dodel et al. (2007) reported reduced

quality of life for people with narcolepsy compared with general population norms based on the SF-36 dimensions and EQ-5D VAS but not the EQ-5D Index.[58] However, narcolepsy patients were more likely to report moderate or severe problems on four of the five EQ-5D dimensions than members of the general public.

Table 27 UK EQ-5D-3L and SF-6D population norms

	EQ-5D-3L index scores		SF-6D	
Age	**Male**	**Female**	**Male**	**Female**
20	0.954	0.932	0.834	0.804
25	0.945	0.924	0.834	0.807
30	0.934	0.913	0.829	0.803
35	0.922	0.901	0.826	0.799
40	0.909	0.887	0.820	0.793
45	0.893	0.872	0.811	0.781
50	0.876	0.855	0.794	0.779
55	0.857	0.836	0.803	0.760
60	0.837	0.816	0.782	0.768
65	0.815	0.794	0.795	0.761
70	0.791	0.770	0.766	0.746
75	0.766	0.745	0.755	0.714
80	0.739	0.718	0.736	0.680

Source: Ara, Brazier and Zouraq 2017[64]and Van Den Berg et al. 2012[65]

ERG conclusions:

- EQ-5D utility estimates reported in the literature for people with narcolepsy are in the range 0.83 to 0.87.
- SF-36 based utilities are lower and more varied (0.59 to 0.76). It is unclear whether any of these values are transferable to a UK setting or UK population preferences.

Table 28 Utility estimates from literature: EQ-5D based

Study, country	Population	Age mean (range)	Study design	Sample	Health states	ESS mean	Utility mean	Limitations
Dodel 2007[58] Germany	Patients with narcolepsy, ICSD criteria	48.9 years (18+)	Cross-sectional survey	N=75	Narcolepsy	NR	0.87	• EQ-5D-3L German value set • Single centre study, Germany • Potential recruitment bias towards more severe disease
Ingravallo 2012[60] Italy	Patients with definite diagnosis of narcolepsy with cataplexy	37.1 years (18-65)	Cross-sectional survey	N=79 N=21	Treated Untreated	13.6 14.0	0.87 0.87	• EQ-5D-3L, value set not stated but refers to Savoia et al. 2006 (UK value set) • Single centre study • Potential recruitment bias • Limitations in reporting
Govi 2016[59] Italy	Patients with type I/II narcolepsy	37.4 years (18-65)	Cross-sectional survey	N=108	Narcolepsy	NR	0.86	• EQ-5D version and value set not reported • Setting not stated • Limitations in reporting
Dauvillers 2017[57] France	Patients with narcolepsy type I and history of cataplexy	41.5 years (adults)	Questionnaire validation (NSS): cross-sectional and before-after	N=175 (134 baseline only / 41 with follow up)	Untreated Treated	17.62 / 18.71 13.83 / 14.02	0.87 / 0.83 0.86 / 0.86	• EQ-5D-3L, value set not specified • Single centre study

Source: CS Appendix H, Table 102, adapted by ERG

Table 29 Utility estimates from literature: SF-36 based

Study, country	Population	Age mean (range)	Study design	Sample	Health states	ESS mean	Utility mean	Limitations
Lanting et al. 2014[44] UK	Patients with diagnosis of narcolepsy (ICSD)	47 years (20-78)	Cost-utility study with data from cross-sectional survey (Teixera 2004)[48]	N=49	Treated (stimulants and/or anti-cataplexy drugs)	19	0.76	• Mapping from SF-36 dimensions to EQ-5D (UK value set)[47] • UK setting (Edinburgh) • Single centre study
Flores, 2016[63] and Villa, 2015[66] US	Adults with diagnosis of narcolepsy and matched controls	47 years (18+)	Case-control burden-of-illness (US NHWS data)	N=437 N=874	Patients with narcolepsy Controls	NR NR	0.59 0.68	• SF-36 valuation method not reported • US NHWS data, unclear if generalisable to UK setting • Potential recruitment bias due to internet-based sampling • Limitations in reporting
Bolin 2017[62] Sweden	Patients with narcolepsy treated for cataplexy and EDS	NR (NR)	Cost-utility study with data from 6-month open-label trial (Hayduk 2001)[67]	N=163-165	Sodium oxybate + venlafaxine Methylphenidate + venlafaxine	NR NR	0.73 0.66	• SF-6D valuation (UK general population)[68] • Swedish cost-effectiveness study with Danish data; unclear if generalisable to UK setting • Limitations in reporting

Source: CS Appendix H, Table 102, adapted by ERG

4.2.7.2 Trial-based health related quality of life

The mean baseline EQ-5D index score in TONES 2 (mITT population) was [redacted].

The company do not use EQ-5D utility results in the economic model base case or scenarios. The company report that no meaningful trends were observed for mean changes from baseline to 12 weeks in EQ-5D-5L index scores for any solriamfetol dose compared with placebo (CS Table 16). They speculate that

> "*this may reflect an inability of this generic HRQoL measure to fully detect the impact of narcolepsy on patient QoL in this particular study design, or may be due to other factors*" (CS B.2.6.8)

and go on to argue that this is an anomaly because

> "*A number of other subjective and objective measures were collected during TONES 2, including ESS, MWT, FOSQ-10, SF-36v2, PGI-c, CGI-c and WPAI. All of these parameters showed improvements from baseline through to week 12, and in change from baseline versus placebo – either in global scores or in specific domain scores – when EDS in patients with narcolepsy was treated with solriamfetol*" (CS B.3.4.1).

However, we note that none of the summary quality of life outcomes reported in CS Table 16 show significant differences in change from baseline to week 12 for the solriamfetol 75 mg or 150 mg groups compared with placebo. We illustrate the trends over time for these outcomes in Figure 8 to Figure 11 below (results extracted from CSR by ERG).

[redacted]

Figure 8 FOSQ change from baseline, TONES 2 mITT population

Source: Extracted from CSR Table 14.2.6.2 by ERG

Figure 9 EQ-5D index score change from baseline, TONES 2 mITT population

Source: Extracted from CSR Tables 14.2.10.2 by ERG

Figure 10 SF-36 PCS change from baseline, TONES 2 mITT population

Source: Extracted from CSR Table 14.2.7.2 by ERG

Figure 11 SF-36 MCS change from baseline, TONES 2 mITT population

Source: Extracted from CSR Table 14.2.7.2 by ERG

The company suggests various possible reasons for the absence of evidence of an effect of solriamfetol on utility based on the TONES 2 EQ-5D results, including: the lack of a sleep or wakefulness domain; the lack of a social relationships domain; high baseline values for EQ-5D indicating that the measure may not capture the problems related to the disease; patient adapation to living with narcolepsy; levels of depression in the trial population that might not have been adequately treated; differences in driving regulations and impact on mobility for US patients in the trial; and better pain management for the US patients.

In response to a clarification question, the company provided graphs of EQ-5D-5L index scores from TONES 5 (Clarification Response Figures 4 and 5).

[redacted]. However, these results include patients treated with the unlicensed 300 mg dose of solriamfetol, and we do not know how utilities would have changed for patients treated with usual care over this time.

ERG conclusions:

Baseline EQ-5D utility for the TONES 2 population was [redacted]

- The company report that the EQ-5D failed to detect a sustained benefit of solriamfetol 75 mg or 150 mg compared with placebo over 12 weeks. In justification of their decision not to use trial utility values in the economic model, the company argue that high baseline EQ-5D values leave little headroom for improvement and that the EQ-5D is insensitive to important aspects of quality of life relevant to narcolepsy. They further suggest that patients adapt their lifestyle and expectations and differences between the US and UK context.
- We agree that these may well be factors but note a similar lack of significant treatment effect with other quality of life measures (FOSQ-10 and SF-36 PCS and MCS). It is likely that the trial would not have been powered to detect changes in quality of life.

4.2.7.3 Mappings from ESS to utility scores

As an alternative to directly measured EQ-5D values from the trial or published literature, the company used a mapping approach to estimate utilities for the model.

4.2.7.3.1 McDaid et al. 2007 algorithm

For TA139, McDaid et al. used a regression approach to estimate change in utility associated with change in ESS.[45] They used individual patient data from three cohorts: two with SF-6D utility estimates (n=294), with values based on UK public preferences[68]; and one with with EQ-5D-3L 'UK Tariff' values (n=94).[61] They used a simple linear regression, as the model fit was not improved with a GLS gamma regression and they did not find evidence that the ESS-utility relationship differed for different baseline levels of ESS. The results are reported in CS Table 42. The SF-6D and EQ-5D models produced very similar estimates of the fall in utility associated with a one-point increase in ESS (0.010).

The obvious limitation in applying the McDaid algorithm in the present appraisal is that it is estimated with data from people with OSA and not narcolepsy. Lanting and colleagues from PenTAG set a precedent by using the McDaid algorithm in a narcolepsy model, arguing that there is no reason to believe that the relationship between ESS and utility change is disease-specific.[44] In support of this, they cited expert opinion and noted that Dodel et al (2007) had failed to detect a relationship between quality of life and cataplexy symptoms or nocturnal sleep quality.[58]

4.2.7.3.2 NHWS mapping

The CS reports a new analysis to investigate the relationship between ESS and EQ-5D utility (CS B.3.4.3 and Appendix M). This used individual-level data from the National Health and Wellness Survey (NHWS) 2016. The sample, recruited from online panels in five EU countries, including the UK, who reported experience of OSA and/or narcolepsy in the past 12 months: 2,348 people[redacted].

The process of data analysis and model fitting is well described, generally following the process for fitting mapping equations recommended by the NICE Decision Support Unit (DSU).[69] The NHWS analysis included

[redacted]

[redacted].

The final model is shown in CS section B.3.4.3 and illustrated in CS Figure 19. It includes a 'break-point', with greater change in utility per unit change in ESS for ESS scores above 11 (coefficient [redacted]) than for ESS scores less than or equal to 11 (coefficient [redacted]). As shown in CS Figure 19, the equation predicts higher utility values over the range of ESS than the McDaid algorithm. The equation adjusts for a wide range of variables, including [redacted]. These include variables that one might not want to adjust for, from an equity point of view (e.g. income and marital status). It is possible that these are mediators of the effect of EDS on utility. The company note that there may be other confounding variables that have not been accounted for.

In practice, values are not available from TONES data for most of the co-variates. Instead, the model uses average values for these variables from the NHWS cohort (with coefficients for OSA with/without narcolepsy set to zero). This means that the model estimates utility as a function of age and sex (defined as input parameters for the model cohort, with increasing age over time) and treatment-related ESS score, with a fixed term reflecting a background level of utility. This absolute utility constant might not reflect utility for the UK narcolepsy population. However, this does not matter because in the absence of a survival difference between the treatments, cost-effectiveness will be driven by between-treatment differences in utility, not by absolute utility values.

4.2.7.4 Utility values used in the model

The company uses the NHWS mapping in their base case and the McDaid algorithm in a scenario. The base case values in treatment initiation are reported in CS Table 43 (Table 25 above). These values are much lower than EQ-5D UK population norms (Table 27) and values reported in the literature for people with narcolepsy (Table 28). In the McDaid algorithm scenario, utilities are calculated as an ESS-related decrement from general population norms, so they are much higher the NHWS estimates.

ERG conclusions

- TONES 2 did not detect a significant effect on the EQ-5D Index: possibly because the EQ-5D is insensitive to the effect of daytime sleepiness, a lack of power in the trial and/or study period being too short for changes to ingrained behaviour or expectations to occur. Or possibly because the effect of solriamfetol on quality of life is insufficient. We note that the trial also failed to show a statistically significant effect on other quality of life measures (EQ-5D VAS, SF-36 PCS and MCS and the disease-specific FOSQ-10).
- There is a paucity of other utility data from the literature that could have been used in the model. Published EQ-5D utilities for narcolepsy are consistent, similar to or a little lower than general population norms, but similar for treated and untreated cohorts. Utility estimates based on the SF-36 have been more varied, but do not meet NICE reference case requirements.
- In this situation, it is reasonable to consider a mapping approach, although this does introduce additional uncertainty. This suggests that EQ-5D data from the TONES trials should have been used to inform the economic analysis. The McDaid algorithm found a consistent estimate of the relationship between utility and ESS across EQ-5D and SF-6D datasets. But it is based on data for people with OSA, not narcolepsy.
- The NHWS mapping from ESS to EQ-5D has some advantages. The methods of analysis are well reported and appeared to be thorough. The dataset is large and, though mostly OSA, it does include a small sample of people reporting narcolepsy. The sample may be subject to recruitment bias due to the use of online sample and self-reporting of diagnosis. So, it is not clear whether the estimation sample is sufficiently similar to the target sample of people with narcolepsy in the UK.
- Utilities estimated by applying the NHWS formula to ESS changes in TONES 2 are much lower than UK general population norms, EQ-5D index scores from TONES 2 and 5 and values for narcolepsy reported in the literature: so, may lack face validity. However, as there is no assumed difference in survival between arms, the absolute utility does not drive the cost-effectiveness results and the NHWS estimate of the change in utility associated with a one-unit change in ESS on utility are reasonably consistent with the McDaid estimates.
- On balance, we agree with the company’s use of the NHWS mapping algorithm in their base case, with the McDaid formula in a scenario.

4.2.8 Resources and costs

The systematic literature review conducted by the company did not identify any UK-based studies for healthcare resource use or costs for patients with narcolepsy. In addition to the systematic review, the company conducted database searches supplemented by hand searching (as described in CS Appendix I). No relevant evidence was found.

4.2.8.1 Drug acquisition

Characteristics of the treatment regimens and unit costs for the therapies included in the analysis are shown in Appendix 9 Table 44 - Table 48. In the company's base case, the cost of each treatment is assumed to be accrued for a minimum of 8 weeks, at which point an assessment of treatment response is conducted and treatment is stopped in non-responders or continued for life in responders unless they experience loss of response or discontinue treatment due to AEs.

Solriamfetol

In clinical practice, doses in narcolepsy patients are titrated to achieve a balance between a good level of improvement and function and treatment side effects. It is likely, however, that more patients will be given higher doses of treatment. Therefore, assuming a higher than 50% market share for solriamfetol 150 mg in the combined analysis (see section 5.1) would be more relevant to UK clinical practice.

Both doses of solriamfetol are costed according to the trial protocol (see Appendix 9). For the base case, the drug acquisition cost for the 150 mg dose is estimated assuming that patients are given 75 mg tablets in the first 3 days and 150 mg dose thereafter (Table 44).

Comparators

The unit costs of all comparator treatments were taken from the National Drug Tariff (Appendix 9 Table 45 - Table 48).[70]

Pilotisant

The costs of treatment with pitolisant during the titration phase (weeks 1 – 8) and maintenance phase (weeks 8+) are shown in Appendix 9 Table 46, and the titration strategy is described in Appendix 9 Table 44. The cost accrued in the maintenance phase is estimated assuming that approximately one third of patients receive 18 mg per day and two thirds are given 36 mg dose.[71] In a one-way sensitivity analysis conducted by the company,

the proportion of patients on 18 mg dose was found to be one of the most influential model parameters (see section 5.2).

We note in the SmPC for pitolisant[72] that the dose can be decreased to 4.5 mg per day, but this is not taken into consideration in the company's analysis. We conducted exploratory analyses assuming that from 10% to 30% of patients are given the lowest (4.5 mg) dose of pitolisant during the maintenance phase - the cost-effectiveness outcome did not change, and therefore, we do not include this dose in our analysis.

Sodium oxybate

In the company's ITC, three doses of sodium oxybate are considered: 4.5 g, 6 g and 9 g (see section 3.4 above and Appendix 9 Table 44 - Table 45), and as for solriamfetol, the base case results are presented separately for each dose as well as for a combination of doses assuming equal split due to the lack of evidence on the proportion of patients who would reach the respective final doses. In the base case (see section 5.1), the cost of this treatment is derived assuming titration as described in CS page 179 and Appendix 9 Table 44.

The acquisition cost of sodium oxybate is likely to be slightly underestimated since patients randomised to this treatment in the trials used in the ITC (Xyrem 2005 and Black 2006) were not titrated onto the assigned study dose (i.e. treatment did not start with the recommended dose of 4.5 g once daily but with the assigned dose). CS Section B.2.9.4 gives further details on the use of non-recommended dosing in the trials included in the ITC.

Dexamfetamine

Recommended use of dexamfetamine is described in Appendix 9. The cost of this treatment is estimated assuming the dose of 40 mg per day and unit costs for the tablet formulation (Appendix 9 Table 47). Dexamfetamine is also available as an oral solution which is not included in the model since this formulatioin is rarely used in clinical practice.

Methylphenidate

The company assume that only modified release preparations of methylphenidate (capsules or tablets) are used in UK clinical practice (see Appendix 9 Table 48). Our clinical expert disagrees with this statement. We also note that according to CS KOL Clinical Practice Interviews, clinical opinion varies as to which preparations are commonly used (tablets or modified release preparations). No sensitivity analyses have been conducted by the

company to quantify the effect of variation in the unit costs of methylphenidate on the outcomes.

According to the company's results (see section 5.2.3), this comparator is likely to be cost-effective. Therefore, assuming the lowest unit cost for methylphenidate (i.e. the cost of tablet) would further improve the cost-effectiveness of this comparator.

Concomitant medications

TONES 5 CSR Table 14.1.9.1a reports concomitant medications used in the safety population in the open label phase of this trial. We note that concomitant treatments were also used in the comparator trials (see section 3.3.4 above). In the company's analysis, however, concomitant medications are not considered.

Other costs

In the company's base case, a general practitioner (GP) contact (at £37 per contact) is included for all AEs leading to discontinuation (CS section B.3.5.2 and CS Table 46).

ERG conclusions:

- Drug acquisition cost is the only cost category modelled in the company's analysis. In the base case, treatment is costed up to week 8 in all patients.
- The acquisition costs for all treatments except methylphenidate are estimated assuming titration, as described in the respective SmPCs. Methylphenidate is costed based on EFNS recommendations.

As previously stated (see section 4.2.4), assuming a higher than 50% market share for solriamfetol 150 mg would be more relevant to UK clinical practice.

Based on clinical advice to the ERG, the modelled equal shares for sodium oxybate 4.5 g, 6 g and 9 g doses, and the assumption that one third of patients receive 18 mg/day and two thirds are given 36 mg/day of pitolisant are reasonable.

4.2.8.2 Drug administration

The treatments considered in this appraisal are taken orally and, therefore, do not incur any administration costs.

4.2.8.3 Resource use

The company do not model healthcare resource use because they assume that patients with narcolepsy are monitored during regular follow-up visits and there are no additional costs beyond those that would be incurred during regular appointments.

We note that the TONES 5 CSR contains information on the number of physician visits, collected via a questionnaire, and the mean healthcare costs incurred by patients on different doses of solriamfetol. The mean numbers and types of specialist appointments are shown in Appendix 10 Table 49 - Table 53. As seen in Table 54 (Appendix 10), there was a trend towards [redacted] estimated healthcare costs in patients treated with solriamfetol 150 mg compared to the costs incurred by patients on the 75 mg dose (the costs are in USD 2018). It should be noted that the TONES 5 trial did not have patients from the UK (see Table 5 above), and the estimated costs might not apply in the NHS.

Expert advice to the ERG suggests that there is a substantial variation in the frequency of doctor appointments for narcolepsy in UK clinical practice. Patients responding to treatment usually have annual reviews once medication is stable, while non-responders are seen more often (every 6 weeks – 3 months) as different medications or combinations of medications are tried. According to South East London Shared Care Prescribing Guidelines,[73] 6 - 12 monthly clinic appointments are recommended for patients with narcolepsy treated with either sodium oxybate or methylphenidate.

Since the healthcare resource use depends on response and treatment dose (as explained above), we include this cost component in our analysis (see section 6). Following clinical advice, we assume in the base case that the frequency of doctor appointments in non-responders is one visit per 3 months, and we test the alternative assumption, six-monthly visits, in a scenario analysis. For responders, parameterisation is done as follows: we assume that patients receiving placebo have annual appointments, while for patients on the other treatments, the frequency of visits is adjusted proportionally to the relative risk (RR) of serious TEAEs with respect to placebo (see Table 22). The frequency of appointments per model cycle (of 1 year) are shown in Table 30.

Table 30 Frequency of outpatient appointments

Treatment	Number of doctor appointments (per year)
Solriamfetol 150 mg	3
Solriamfetol 75 mg	1
Pitolisant ≤40 mg	0.97
Sodium Oxybate 4.5 g	2.65
Sodium Oxybate 6 g	2.86
Sodium Oxybate 9 g	3.27

Note: based on the ITC results for RR of serious TEAEs with respect to placebo (Table 22)

According to the CS KOL Clinical Practice Interviews, all appointments for patients with narcolepsy are consultant-led. We have been advised by our clinical expert that in clinical practice this will depend on the set up and size. The cost of a follow-up outpatient visit with specialist (£108) was assumed in TA139.[4] In our analysis, we use the same approach and estimate the cost of doctor appointments in each treatment arm assuming the unit cost of £130 per outpatient visit with specialist (which is the units cost of £108[4] inflated to 2019-2020 prices using the Hospital and Community Health Services (HCHS) pay and prices index.[74]

Costs of managing adverse events

In the company's analysis, the cost of managing AEs is not included because, as the company state, the incidence of TEAEs in the trials was similar across all treatments analysed (see CS Appendix D Table 38).

We note that in TONES 5, [redacted] (as shown in Appendix 10 Table 55): [redacted]. The respective proportions of patients hospitalised due to SAEs in TONES 5 (assuming one hospitalisation per patient) are [redacted]% and [redacted]% per [redacted] weeks (the weighted average duration of follow-up across groups A and B, see Table 54). Hence, the estimates suggest that hospitalisation in TONES 5 participants was [redacted], although they are subject to uncertainty due to small sample size. We note that the hospital admissions in TONES 5 were for [redacted] (see Appendix 10 Table 55).

One subject from the solriamfetol 150 mg arm of TONES 2 (n = 55) was hospitalised due to a SAE; there were no hospitalisations for SAEs in the 75 mg study arm (n = 59).

In our analysis, we derive the proportion of patients who would require hospitalisation due to serious AEs for solriamfetol 75 mg and comparator arms from the estimate for solriamfetol 150 mg and the RRs for serious TEAEs (shown in Table 22). Due to the lack of long-term evidence, we follow the same approach used by the company when estimating the rate of discontinuation due to AEs (see section 4.2.6.2 above), and calculate the hospitalisation rates in subsequent years as 43.2% of those in the first year. Estimated hospitalisation rates per model cycle (of 1 year) are presented in Table 31.

Table 31 Proportion of patients hospitalised per model cycle

Treatment	Hospitalisation (per year)	
	First year	Subsequent years
Solriamfetol 150 mg	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]
Pitolisant ≤40 mg	[redacted]	[redacted]
Sodium Oxybate 4.5 g	[redacted]	[redacted]
Sodium Oxybate 6 g	[redacted]	[redacted]
Sodium Oxybate 9 g	[redacted]	[redacted]

A mean hospital stay of 3.5 ± 0.9 days per patient for hospital admission due to narcolepsy was reported in Dodel et al. 2004.[75] The hospitalizations were caused by an adjustment or initiation of therapy (n = 7; 54%), side effects of medication and diagnostic work-up (n = 4; 31%), or accidents directly related to narcolepsy (n = 3; 23%). This study included patients seen in a highly specialized unit. The authors note that selection bias may be possible toward more severely affected patients.

The HRG codes, which we believe are most relevant to hospital admissions due to narcolepsy, are shown in Table 32 below.

Table 32 HRG codes

Currency code	Currency description	National average unit cost (per day)
AA43A	Sleep Disorders, excluding Sleep Apnoea, with CC Score 2+	£2,254
AA43B[a]	Sleep Disorders, excluding Sleep Apnoea, with CC Score 0-1	£1,341

Source: National Schedule of Reference Costs - Year 2018-19 non-elective long stay[76]
[a] For this currency code, the average number of days in hospital (one day) is reported in the National Schedule of Reference Costs - Year 2017-18.[77]

Tests

Ongoing monitoring of patients with narcolepsy include checking weight, blood pressure and heart rate during doctor appointments.

ERG conclusions:

- We note that the company conducted a systematic literature review and other searches for evidence on UK-based studies of healthcare resource use and costs. Since no relevant sources had been found, evidence for other jurisdictions, such as Western European countries, would also be useful to inform the economic analysis.
- The company do not model healthcare resource use and costs, effectively assuming they are the same across all treatment arms. We note in the TONES 5 CSR that the economic outcomes, namely the mean/median healthcare costs over the 1-year period were planned outcomes in this trial. The estimated costs were [redacted] Those costs, however, are not considered in the company's model.
- In UK clinical practice, patients who do not respond to therapy are seen by clinicians considerably more often compared to those who respond. In our analysis, we include the costs of consultant-led appointments, and hospitalisation due to TEAEs (based on the TONES studies), stratified by treatment and response status and estimated over the model time horizon (Table 30 - Table 32). It should be noted that based on clinical input, AE-related hospitalisation in patients treated for EDS due to narcolepsy is rare in UK clinical practice.

In the base case, we assume that the average hospital stay is 3.5 days[75] (see section 6), and we test the impact of the alternative assumption of 1 day per hospital stay (as shown in Table 32) in a scenario analysis (section 6); the unit cost of £1,341/day (Table 32) is assumed in both analyses.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The results of the company's base case analysis are presented in CS Section B.3.7. They consist of two sets of results for a bootstrap sampling of IPD data and a deterministic analysis based purely on individual patent level solriamfetol 150 mg data and the associated

pseudo-IPD for the comparators. For these two sets of analysis, the company provides separate cost-effectiveness results comparing individual treatment doses and for combined doses. In the cost-effectiveness analysis for combined doses, costs and QALYs for solriamfetol 75 mg and 150 mg are combined based on an assumption of 50% market share while costs and QALYs for sodium oxybate 4.5mg, 6mg and 9mg are combined based on a 33% market share assumption. Results for the company's bootstrap sampling (CS Tables 48 and 50) are presented in Table 33 and Table 34 below.

Table 33 Company base case results by dose based on bootstrap sampling

Drugs	Total costs (£)	Total QALYs	Incremental ICER (£/QALYs)	ICER versus solriamfetol 75 mg (£/QALY)	ICER versus solriamfetol 150 mg (£/QALY)
Solriamfetol 75 mg	£5,975 (£5,974 - £5,977)	13.273 (13.270 - 13.275)			£70,702*
Solriamfetol 150 mg	£10,766 (£10,765 - £10,767)	13.341 (13.338 - 13.343)	£70,702	£70,702	
Sodium Oxybate 4.5 g	£11,473 (£11,468 - £11,477)	13.203 (13.201 - 13.206)	Dominated	Dominated	Dominated
Pitolisant 40 mg	£20,991 (£20,990 - £20,992)	13.341 (13.338 - 13.344)	£69,120	Extendedly dominated	Extendedly dominated
Sodium Oxybate 6 g	£22,587 (£22,581 - £22,593)	13.272 (13.269 - 13.274)	Dominated	Dominated	Dominated
Sodium Oxybate 9 g	£43,532 (£43,530 - £43,534)	13.346 (13.344 - 13.349)	£280,171	£509,641	£5,521,622*

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. * South-West Quadrant of the cost-effectiveness plane. Note, the quadrant represents the position of Solfiamfetol 150 mg with respect to a comparator.
Source: Adapted from CS Table 48

Table 34 Company base case results for combined doses with bootstrap sampling

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,371	13.307	42.044			
Pitolisant	£20,991	13.341	42.044	£12,620	0.034	£367,593
Sodium oxybate	£25,864	13.274	42.044	£4,873	-0.067	Dominated

Source: CS Table 49
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The ERG notes that the company's estimation of incremental ICERs in Table 33 (third column from the right) are incorrect for all treatments except solriamfetol 75 mg. Sodium oxybate 4.5mg, pitolisant 40 mg and sodium oxybate 6mg are dominated or extendedly dominated while sodium oxybate 9 g has a ICER of £5,521,622 per QALY gained. The two last columns are mislabelled as incremental analysis but are actually pairwise comparisons and therefore extended dominance does not apply.

Company base case results based on analysis of raw IPD solriamfetol 150 mg data and the associated pseudo-IPD for the comparators (CS Tables 50 and 51) are presented below in Table 35 and Table 36.

Similar to Table 33, the ICER presented for treatments in Table 35 are incorrect for all treatments except solriamfetol 75 mg. Sodium oxybate 4.5mg, pitolisant 40 mg and sodium oxybate 6mg are dominated or extendedly dominated while sodium oxybate 9 g has a ICER of £5,521,510 per QALY gained. The cost-effectiveness ratios in the last column are also pairwise and as such, extended dominance is not applicable.

Table 35 Company base case results for separate doses based on raw IPD

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus solriamfetol 75 mg (£/QALY)
Solriamfetol 75 mg	£5,974	13.335				
Solriamfetol 150 mg	£10,766	13.403	£4,793	0.068	£70,681	£70,681
Sodium Oxybate 4.5 g	£11,469	13.265	£703	-0.137	Dominated	Dominated
Pitolisant <40 mg	£20,991	13.403	£9,522	0.138	£69,136	Extendedly dominated
Sodium Oxybate 6 g	£22,580	13.334	£1,589	-0.069	Dominated	Dominated
Sodium Oxybate 9 g	£43,532	13.409	£20,952	0.075	£280,091	£509,340

Source: CS Table 50
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 36 Company base case results for combined doses based on the raw IPD

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,370	13.369			
Pitolisant	£20,991	13.403	£12,621	0.034	£367,368
Sodium oxybate	£25,860	13.336	£4,870	-0.067	Dominated

Source: CS Table 51
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Cost-effectiveness results for the bootstrap sampling analysis mirror those of the raw IPD analysis with ICERs for solriamfetol 150 mg compared to baseline (solriamfetol 75 mg) estimated to be £70,702 and £70,681 respectively. Sodium oxybate had an ICER exceeding £5,000,000 per QALY gained while other comparators were either dominated or extendedly dominated. Results for the combined cost-effectiveness analysis compared three treatments: solriamfetol, pitolisant and sodium oxybate. The bootstrap sampling analysis and raw IPD analysis show similar results with sodium oxybate dominated and ICERs of £367,593 and £367,368 respectively for pitolisant.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analysis

The company explored parameter uncertainty with one-way sensitivity analysis by varying parameters of interest over the 95% CI of their individual point estimates or extremes of +/- 20% where precision estimates were not available. Parameter uncertainty is presented in tornado plots (CS Figure 22 and 23) and tables of univariate analysis for both pitolisant and sodium oxybate compared with solriamfetol (CS Tables 53 and 54). These figures and tables show the parameters with the greatest impact on cost-effectiveness. The ERG spotted an error in the company's model (clarification question B10) that produced different sets of results when we reran the model. The company clarified the source of the discrepancy and ERG has been able to reproduce the results in the CS. These results show that assumptions around the dosing of pitolisant and sodium oxybate, the changes in ESS relative to solriamfetol 150 mg for pitolisant and sodium oxybate and the proportion of patients assumed to receive specific doses of solriamfetol or sodium oxybate were the biggest drivers of cost-effectiveness. However, none of these results produced a net monetary benefit (NMB) below £0 at a willingness to pay threshold of £20,000 per QALY gained for either lower or upper bound parameter assumptions. An NMB below £0 indicates that the

treatment is not cost-effective at the stated threshold. The results from the CS are reproduced below in Table 37 and Table 38.

Table 37 CS Results of univariate analysis: solriamfetol vs pitolisant

Variable (lower bound to upper bound; base case value)	Net monetary benefit with lower bound	Net monetary benefit with upper bound
Dosing: Pitolisant 18 mg (Week 8+) (0.0% to 100.0%; base case 33.3%)	£16,013	£3,776
Change in ESS relative to Sol 150 mg: Pitolisant (-2.279 to 2.377; base case 0.050)	£4,712	£16,408
Discount rate: Costs (0.0% to 6.0%; base case 3.5%)	£14,519	£10,606
Proportion of patients on Sol 75 mg (0.0% to 100.0%; base case 50.0%)	£10,216	£13,652
Discontinuation - LoE (Yr n): Pitolisant (8.7% to 13.1%; base case 10.9%)	£13,648	£10,559
Discontinuation - TEAEs (Yr n): Pitolisant (3.5% to 5.3%; base case 4.4%)	£12,531	£11,384
Discontinuation - LoE (Yr 1): Pitolisant (8.7% to 13.1%; base case 10.9%)	£12,269	£11,599
Discontinuation - LoE (Yr n): Sol 150 mg (8.7% to 13.1%; base case 10.9%)	£11,642	£12,168
Change in ESS relative to Sol 150 mg: Sol 75 mg (-3.456 to -0.137; base case -1.797)	£12,355	£11,863
Dosing: Pitolisant 18 mg (Weeks 3 - 8) (0.0% to 100.0%; base case 33.3%)	£12,030	£11,741

Abbreviations: ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy; Sol, solriamfetol; TEAE, treatment emergent adverse events; Yr 1, Year one; Yr n, Years 2 and beyond.

Table 38 Results of univariate analysis: solriamfetol vs sodium oxybate

Variable (lower bound to upper bound; base case value)	Net monetary benefit with lower bound	Net monetary benefit with upper bound
Proportion of patients on Sodium oxybate 4.5 g (0.0% to 66.7%; base case 33.3%)	£27,880	£8,414
Proportion of patients on Sodium oxybate 6 g (0.0% to 66.7%; base case 33.3%)	£24,633	£11,662
Change in ESS relative to Sol 150 mg: Sodium Oxybate 9 mg (-1.518 to 2.832; base case 0.656)	£15,376	£21,971
Discount rate: Costs (0.0% to 6.0%; base case 3.5%)	£21,741	£16,302
Change in ESS relative to Sol 150 mg: Sodium Oxybate 6 mg (-4.451 to 0.558; base case -1.946)	£14,426	£19,820

Variable (lower bound to upper bound; base case value)	Net monetary benefit with lower bound	Net monetary benefit with upper bound
Change in ESS relative to Sol 150 mg: Sodium Oxybate 4.5 mg (-5.448 to -0.447; base case -2.946)	£16,379	£20,234
Proportion of patients on Sol 75 mg (0.0% to 100.0%; base case yy	£16,429	£19,865
Discontinuation - LoE (Yr n): Sodium Oxybate 9 g (8.7% to 13.1%; base case 10.9%)	£19,564	£17,011
Discontinuation - LoE (Yr n): Sodium Oxybate 6 g (8.7% to 13.1%; base case 10.9%)	£18,829	£17,600
Discontinuation - TEAEs (Yr n): Sodium Oxybate 9 g (3.5% to 5.3%; base case 4.4%)	£18,642	£17,692

Abbreviations: ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy; sol, solriamfetol; Yr 1, Year one; Yr n, Years 2 and beyond

5.2.2 Threshold analysis

The company performed threshold analysis on parameters identified in the one-way deterministic sensitivity analysis to determine at what values the NMB for solriamfetol would no longer be positive at a willingness to pay threshold of £20,000 per QALY gained. Where negative NMBs were estimated, the parameter values assumed were deemed to be implausible.

5.2.3 Scenario analysis

The company conducted a range of scenario analyses (see CS Section B.3.8.4), exploring a longer primary end-point of 12 weeks for the measure of mean ESS, different model time horizons, alternative definitions of response, alternative discontinuation rates, alternative market shares for the different doses of solriafetol and estimates of HRQoL based on the McDaid 2007 study.[45] Cost-effectiveness estimates of these scenarios did not vary significantly from the company's base case analysis.

The company also considered dexamfetamine and methylphenidate in scenario analyses since these treatments were excluded from the ITC due to the lack of evidence (as explained in section 4.2.4 above). The cost-effectiveness results for various doses of methylphenidate MR tablets and capsules against solriamfetol 75 mg and 150 mg were obtained for a range of ΔESS relative to solriamfetol (from -7 to -1) (see CS Tables 79-84).

A range of doses of dexamfetamine (from 10 mg to 60 mg) and ΔESS relative to solriamfetol (from -7 to -1) are considered in the company's scenario analyses (see CS Tables 75-76).

According to the results of the KOL Clinical Practice Interviews, not many patients receive the 60 mg dose of dexamfetamine due to its toxicity.

Cost-effectiveness estimates vary widely across these assumptions. The ERG notes that the choices of ΔESS relative to solriamfetol considered for dexamfetamine and methylphenidate are arbitrary.

5.2.4 Probability sensitivity analysis

An inspection of change in ESS from baseline for solriamfetol 150 mg suggests that the respective distribution is non-normal and skewed to the left (i.e. there were more patients in the pivotal trial who had higher ΔESS than the observed mean). Therefore, we consider that the use of bootstrapping to quantify first-order uncertainty in treatment effectiveness is appropriate. This method, if applied correctly, would allow taking into consideration the impact of higher ΔESS (i.e. changes in ESS from baseline in patients who most benefited from treatment) without making any assumptions on the form of the respective distribution.

The company's bootstrap method consists of two steps. First, 5,000 random samples (described by the company as bootstrap samples) are drawn from the IPD data of 54 patients. Each of these 5,000 draws represent the clinical features estimated for an IPD, including comparator estimates of ESS change from baseline. Finally, 1,000 random samples are drawn from mean parameter estimates of the initial 5,000 'bootstrap' samples. Cost-effectiveness estimates are then derived from these values to produce the company's bootstrap base case results.

The company's PSA is a replication of the 'bootstrap' procedure described above with the application of distributions to additional parameters such as change in ESS relative to solriamfetol 150 mg, excess mortality associated with narcolepsy, costs, resource use, utilities and discontinuation rates. In the company's PSA, 10,000 random samples of parameter means are drawn to calculate a mean. The company does not provide any justification for the number of iterations although it adds considerable computational time (about 1 hour and 30 minutes) to the model runtime. The PSA accounts for the joint uncertainty attributed to most of the model parameters. The ERG finds the choice of distributions used by the company appropriate. The results from the company's PSA analysis matched those of the base cases.

According to Gray et al. 2010[54] (the source cited in the CS) and Efron et al. (who introduced this methodology), bootstrapped samples should be of the same size as the original dataset. Thus, each PSA iteration should combine results from one non-parametric bootstrap sample of the same size as the original TONES 2 150 mg narcolepsy data (n = 54) with one set of random draws from the distributions for other model parameters. Inflating the bootstrap sample size to 5,000 per PSA iteration artificially reduces uncertainty. The ERG is also of the opinion that the uncertainty around change in ESS relative to solriamfetol 150 mg should have been incorporated into the model during the bootstrapping rather than during the PSA.

ERG conclusions:

- The ERG note that the errors in estimation of ICERs in the company's analyses do not change the conclusions on cost-effectiveness and base case estimates for bootstrap analysis and IPD analysis are similar. Scenario and sensitivity analysis do not alter conclusions on cost-effectiveness.
- The ERG is of the opinion that the company's method of bootstrap analysis applies an arbitrary sample size that artificially reduces uncertainty. In the ERG preferred analysis below, we explain our method and apply other corrections as previously noted.

5.3 Subgroup analysis

The company also reports a subgroup analysis considering use of solriamfetol after modafinil use. Clinical data for this analysis is drawn from IPD 40 patients and the results are reported in CS Tables 85 and 86. They show combined and individual doses of solriamfetol to be cost-effective. The ERG also explores this subgroup analysis in section 6 of the ERG report.

5.4 Model validation and face validity check

The company submission states that the model was independently and externally assessed by a senior health economic modeller who checked for errors in the formulas and data inputs. We spotted a few model errors in the company's formulas which we have clarified with the company. A series of white box and black box checks were carried out by the ERG and corrections where made in the company's model. These are reported in Appendix 11 and section 5.4.1 of the ERG submission.

5.4.1 ERG corrections to the company model

Table 39 Corrections to the unit costs of the comparator treatments

Regimen	Drug	Tablets per pack	Pack price (£)	ERG price (£)
Dexamphetamine	5 mg	28	24.70	19.89 [a]
	10 mg	30	39.78	39.64 [b]
Methylphenidate				
modified release capsules	50 mg	30	62.52	49.64 [b]
	60 mg	30	67.32	50.36 [b]
modified release tablets	18 mg	30	31.19	21.53 [b]
	27 mg	30	36.81	26.77 [b]
	36 mg	30	42.45	29.86 [b]

[a] BNF
[b] eMIT(last updated November 2019).

The corrections to costs of Dexamphetamine and Methylphenidate reported in Table 39 are only relevant when the applicable doses are considered in the model. In our scenario analysis, we only consider 40 mg doses and therefore use the prices from the company's model.

In the course of ERG model checks (Appendix 11), we spotted some minor errors which have been addressed in company responses to ERG clarification questions (see clarification questions B10 and B12). Where necessary these corrections have been implemented in the ERG updated version of the company's model.

5.4.2 ERG summary of key issues and additional analyses

Table 40 Summary of key issues in the company's analysis

Issue	Company analysis	ERG comments	ERG analysis
Population			
Population characteristics	Base case: Mean age - 38 years, 70.4% female, ESS score at baseline – 17.1 Scenarios: none	The company use the baseline demographic and disease characteristics of the solriamfetol 150 mg mITT population of TONES 2 for model parameterisation (see Table 23). We believe that the modelled population characteristics should reflect those of the whole eligible population recruited to the pivotal trial (Table 23).	Base case: Mean age – 36.2 years, 65% female, ESS score at baseline – 17.2 Scenario: as in the company's base case
Gender composition	Base case: 70.4% female Scenarios: none	We have been advised by our clinical experts that men and women are equally likely to have narcolepsy and seek treatment. We do not change the base case for the sake of consistency with the clinical data, but we conduct a scenario analysis assuming equal proportions of male and female patients.	Base case: 65% female (as above) Scenario: 50% female
Model time horizon	Base case: a lifetime time horizon Scenarios: 5, 10, 15, and 70 years	We assume the lifetime time horizon in the base case and 1 year (the follow-up period in TONES 5) in a scenario analysis.	Base case: no change Scenario: 1, 5, 15 and 20 years
Clinical effectiveness			
Timepoint / ITC results used in the model	Base case: 8 weeks (fixed effects model) Scenario: 12 weeks (fixed effects model)	We note that 12 weeks was the primary end point in TONES 2, and that using this time point in the economic analysis would introduce inconsistency with the clinical data from the comparator trials, conducted for the maximum of 8 weeks. We also note that extending the time to response assessment beyond 8 weeks in the model would mean that the acquisition costs for patients receiving the	Base case: 8 weeks (random effects model), Table 20 Scenarios: 12 weeks (random effects model), Table 20

		comparator treatments would be overestimated since patients would remain on therapy for longer than the treatment duration in the respective studies. Therefore, we use the same assumption in our base case. However, our preference is in using the ITC results from the random effects model (as explained in section 3.6.4).	
Time to treatment response	Base case: 1 week Scenarios: none	Improvement in ESS and the associated impact on QoL are assumed to occur after 1 week from treatment initiation for all treatments based on evidence from TONES 2. Clinical advice to the ERG suggests that improvements in patients treated with sodium oxybate are usually seen not earlier than 3 months after treatment initiation. A potential scenario analysis assuming the time to treatment response of 3 months for sodium oxybate and 1 week for solriamfetol would increase the incremental QALYs and, as a result, produce a lower ICER, but this would introduce inconsistency between the economic outcomes and the clinical effectiveness evidence for sodium oxybate used in the ITC. Hence, we do not conduct such an analysis for this comparator. We run one scenario to explore the sensitivity of the model results to changes in this parameter: we make a hypothetical assumption that the time to treatment response is 2 weeks for all treatments.	Base case: no change Scenario: 2 weeks

Treatment discontinuation			
due to loss of response	Base case: 10.9% per year for all treatments Scenarios: Discontinuation rates for the comparators from year two onwards are set to: • half the base case value • zero • twice the base case value	In the base case analysis, the company apply the same discontinuation rate, estimated from TONES 5, for all treatments. Uncertainty in this parameter is explored by varying it for the comparator treatments.	Base case: no change Scenarios: no change
due to TEAEs	Base case: 4.4% per year for all treatments Scenarios: Discontinuation rates for the comparators from year two onwards are set to: • half the base case value • zero twice the base case value	The estimate is based on TONES 5. It is assumed that the discontinuation rates for the comparators are equal to that for solriamfetol.	Base case: no change Scenarios: no change
Definition of response	Base case: reduction in ESS≥3 points Scenarios: a reduction in ESS≥2 and ESS≥4 points	Clinical advice suggests that in some patients responding to therapies, change in the ESS is small, and a change of 2-3 would be reasonable. Therefore, we assume a lower reduction in the ESS for our base case.	Base case: reduction in ESS≥2 points Scenarios: a reduction in ESS≥3 and ESS≥4 points
AEs	Base case: not modelled Scenarios: none	The CS reports on hospitalisation in participants from TONES 5 who experienced SAEs. We include the hospitalisation costs in our analyses (see below).	Base case: see below Scenarios: see below
HRQoL estimates	Base case: EQ-5D-3L utility estimates derived from 2016-2017 EU5 NHWS data from 2,348 respondents using a de novo mapping algorithm Scenarios: QoL estimates based on		Base case: no change Scenarios: no change

	the algorithm from McDaid 2007		
Resource use			
The cost of treatment initiation	Base case: the cost of treatment during the initiation phase of 8 weeks for all therapies Scenario: the costs incurred during 12 weeks	As has been stated above, we assume that assessment of treatment response is conducted at week 8 for all treatments, and we estimate acquisition costs based on this assumption.	Base case: no change Scenario: no change
The cost of hospitalisation due to SAEs	Base case: not modelled Scenarios: none	We include this cost component in our analysis. We use the rate of hospitalisation in patients treated with solriamfetol 150 mg, observed in the TONES studies, and the relative risks of serious TEAEs (Table 22) to estimate the hospitalisation rates for the other treatments (including solriamfetol 75 mg). The mean duration of inpatient stay of 3.5 days (Dodel et al. 2004) is applied in the base case, and 1 day (the mean duration of hospitalisation for narcolepsy, HRG code AA43B, Table 32 in a SA. Note that this cost is assumed only in patients receiving treatment. We do not model utility reduction due to hospitalisation since its effect on QALYs is likely to be negligible.	Base case: hospitalisation rates in responders as shown in Table 31, mean duration of a hospital stay – 3.5 days, cost of hospitalisation - £1,341/day Scenario: the same hospitalisation rates and unit cost as in the ERG base case; mean duration of a hospital stay – 1 day
The cost of medical appointments	Base case: not modelled Scenarios: none	Clinical advice to the ERG suggests that responders would have annual reviews once medication is stable; non-responders would be seen more often (every 6 weeks – 3 months). In TONES 5, [redacted] We account for this by estimating the frequency of specialist visits for the other treatments (including solriamfetol 75 mg)	Base case: Non-responders – every 3 months; responders – the frequency of appointments as shown in Table 30; the unit cost - £130 per visit Scenario: non-responders – every 6 weeks, responders – as in the ERG base case

		based on the relative risks of serious TEAEs.	
Market share			
Solriamfetol 75 mg and 150 mg	Base case: a 50/50 split Scenarios: 30/70 and 70/30 split for solriamfetol 75 mg and 150 mg	The company's base case assumption is informed by the current usage of solriamfetol 75 mg and 150 mg doses in the US. Based on the clinical advice to the company (KOL), treatment dose would generally be titrated to maximum dose. Clinical advice to the ERG suggests that considerably more than half of patients are likely to be given the higher dose of solriamfetol.	Base case: 10/90 split for solriamfetol 75 mg and 150 mg Scenarios: as in the company's base case, 20/80 and 0/100 split for solriamfetol 75 mg and 150 mg
Pitolisant	Base case: one third of patients receive 18 mg per day and two thirds are given 36 mg dose in the maintenance phase Scenarios: none	Based on clinical advice, the assumption on split between 18 mg and 36 mg doses is reasonable. We conducted exploratory analyses assuming that from 10% to 30% of patients are given the lowest (4.5 mg) dose of pitolisant during the maintenance phase - the cost-effectiveness outcome did not change.	Base case: no change Scenarios: none
Sodium oxybate 4.5 g, 6 g and 9 g	Base case: equal split Scenarios: none	In the company's analysis, three doses of sodium oxybate are considered: 4.5 g, 6 g and 9 g, and the base case results are presented separately for each dose as well as for a combination of doses assuming equal split. Based on clinical advice, this assumption is reasonable. We conduct additional scenario analyses exploring the effect of 10/10/80 and 0/0/100 split on the results.	Base case: no change Scenarios: 10/10/80 and 0/0/100 split for sodium oxybate 4.5 g, 6 g and 9 g

Abbreviations: ESS Epworth Sleepiness Scale, ITC indirect treatment comparison, SA sensitivity analysis

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 ERG's preferred assumptions

Table 41 Cumulative change from the company to ERG base case

	Treatment	Total Costs	Total QALYs	Pairwise ICER: Sol vs comparator	ICER (QALY)	ICER Rank
Company base case (ERG corrected: cost of non-responders in subsequent years)	Solfiamfetol	£8,365	13.369	Reference	Reference	1
	Pitolisant	£20,985	13.403	£367,349	£367,349	2
	Sodium oxybate	£25,856	13.336	-£532,732	Dominated	
+ Population characteristics: Base case: Mean age - 36.2 years, 65% female, ESS score at baseline – 17.2	Solfiamfetol	£8,369	13.487	Reference	Reference	1
	Pitolisant	£20,995	13.522	£362,869	£362,869	2
	Sodium oxybate	£25,868	13.454	-£525,380	Dominated	
+ ITC results: ERG ITC results?	Solfiamfetol	£8,369	13.487	Reference	Reference	1
	Pitolisant	£19,246	13.495	£1,371,635	£1,371,635	2
	Sodium oxybate	£25,868	13.454	-£523,944	Dominated	
+ Definition of response	Solfiamfetol	£9,549	13.517	Reference	Reference	1
	Pitolisant	£20,995	13.515	-£6,224,285	Dominated	
	Sodium oxybate	£30,405	13.483	-£611,849	Dominated	
+ Resourse use: The cost of hospitalisation due to SAEs: mean duration 3.5	Solfiamfetol	£9,983	13.517	Reference	Reference	1
	Pitolisant	£21,191	13.515	-£6,094,960	Dominated	
	Sodium oxybate	£31,187	13.483	-£622,070	Dominated	
+ The cost of medical appointments: responders	Solfiamfetol	£10,910	13.517	Reference	Reference	1
	Pitolisant	£21,607	13.515	-£5,817,607	Dominated	
	Sodium oxybate	£32,600	13.483	-£636,350	Dominated	
+ The cost of medical appointments: non-responders: 4	Solfiamfetol	£20,447	13.517	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£5,830,957	Dominated	
	Sodium oxybate	£42,309	13.483	-£641,392	Dominated	
+ Market share - Solriamfetol 75 mg 10%	Solfiamfetol	£23,086	13.547	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£253,654	Dominated	
	Sodium oxybate	£42,309	13.483	-£299,829	Dominated	
ERG base case	Solfiamfetol	£23,086	13.547	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£253,654	Dominated	
	Sodium oxybate	£42,309	13.483	-£299,829	Dominated	

In Table 41 above, we present our base case results which we estimate by making cumulative assumptions and ERG corrections to the company's model. We present pairwise cost-effectiveness comparisons of the combined doses of solriamfetol (10% market share for 75 mg) versus pitolisant and the combined doses of sodium oxybate (according to the company's base case analysis. Solriamfetol dominates both treatments in the ERG base.

6.2 Scenario analyses undertaken by the ERG

Table 42 ERG scenario analyses

Scenarios	Treatment	Total Costs	Total QALYs	Pairwise ICER: Sol vs comparator	ICER (QALY)	ICER Ranking
Population characteristics: 50% female	Solfiamfetol	£22,980	13.621	Reference	Reference	1
	Pitolisant	£31,056	13.589	-£253,659	Dominated	
	Sodium oxybate	£42,185	13.557	-£299,829	Dominated	
Model time horizon: 1 years	Solfiamfetol	£1,545	0.330	Reference	Reference	1
	Pitolisant	£2,484	0.327	-£297,959	Dominated	
	Sodium oxybate	£3,528	0.323	-£300,297	Dominated	
Model time horizon: 5 years	Solfiamfetol	£9,189	2.684	Reference	Reference	1
	Pitolisant	£14,027	2.665	-£257,024	Dominated	
	Sodium oxybate	£20,580	2.646	-£299,866	Dominated	
Model time horizon: 15 years	Solfiamfetol	£17,022	7.109	Reference	Reference	1
	Pitolisant	£24,663	7.079	-£253,941	Dominated	
	Sodium oxybate	£35,178	7.049	-£299,833	Dominated	
Model time horizon: 20 years	Solfiamfetol	£18,827	8.751	Reference	Reference	1
	Pitolisant	£26,750	8.720	-£253,754	Dominated	
	Sodium oxybate	£37,663	8.688	-£299,830	Dominated	
Clinical efectiveness: time point (12 weeks)	Solfiamfetol	£22,777	13.545	Reference	Reference	1
	Pitolisant	£26,883	13.463	-£50,237	Dominated	
	Sodium oxybate	£36,322	13.442	-£131,008	Dominated	
Time to treatment response (2 weeks)	Solfiamfetol	£23,086	13.547	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£253,654	Dominated	
	Sodium oxybate	£42,309	13.483	-£299,829	Dominated	
Treatment discontinuation multipliers due to loss of response and TEAEs: 0.5x	Solfiamfetol	£23,086	13.547	Reference	Reference	1
	Pitolisant	£42,267	13.670	£155,878	£155,878	2
	Sodium oxybate	£59,750	13.620	£504,202	Dominated	
Treatment discontinuation multipliers due to loss of response and TEAEs: 0x	Solfiamfetol	£23,086	13.547	Reference	Reference	1
	Pitolisant	£82,850	14.237	£86,669	£86,669	2
	Sodium oxybate	£123,527	14.120	£175,265	Dominated	
Treatment discontinuation	Solfiamfetol	£23,086	13.547	Reference	Reference	1
	Pitolisant	£23,625	13.410	-£3,936	Dominated	

Scenarios	Treatment	Total Costs	Total QALYs	Pairwise ICER: Sol vs comparator	ICER (QALY)	ICER Ranking
multipliers due to loss of response and TEAEs: 2x	Sodium oxybate	£30,454	13.390	-£46,898	Dominated	
Definition of response: reduction in ESS≥4 points	Solfiamfetol	£20,689	13.492	Reference	Reference	1
	Pitolisant	£26,760	13.461	-£197,513	Dominated	
	Sodium oxybate	£33,835	13.424	-£195,114	Dominated	
The cost of medical appointments applied every 6 weeks for non-responders	Solfiamfetol	£34,014	13.547	Reference	Reference	1
	Pitolisant	£42,332	13.515	-£261,029	Dominated	
	Sodium oxybate	£53,644	13.483	-£306,177	Dominated	
Market share - Solriamfetol 75 mg 20%	Solfiamfetol	£22,426	13.540	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£358,903	Dominated	
	Sodium oxybate	£42,309	13.483	-£351,247	Dominated	
Market share - Solriamfetol 75 mg 0%	Solfiamfetol	£23,745	13.555	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£188,538	Dominated	
	Sodium oxybate	£42,309	13.483	-£259,191	Dominated	
Market share - Sodium oxybate 4.5 mg 10% and Sodium oxybate 6mg 10%	Solfiamfetol	£23,086	13.547	Reference	Reference	1
	Pitolisant	£31,169	13.515	-£253,654	Dominated	
	Sodium oxybate	£55,611	13.538	-£3,493,589	Dominated	
Prior modafinil	Solfiamfetol	£22,434	13.535	Reference	Reference	1
	Pitolisant	£30,480	13.510	-£319,536	Dominated	
	Sodium oxybate	£40,534	13.480	-£329,595	Dominated	
ERG base case including methylphenidate (40 mg) and dexamfetamine (40 mg)	Methyl-phenidate	£1,676	13.413	£159,820	Reference	1
	Dex-amfetamine	£4,074	13.413	£141,921	Dominated	
	Solfiamfetol	£23,086	13.547	Reference	£159,820	2
	Pitolisant	£31,169	13.515	-£253,654	Dominated	
	Sodium oxybate	£42,309	13.483	-£299,829	Dominated	

In Table 42, we explore different scenarios and consider a subgroup analysis for IPD who received prior modafinil. We also include methylphenidate and dexamfetamine as comparators. Except for the scenario where methylphenidate and dexamfetamine are included, all of the above scenarios show solriamfetol to be cost-effective at a threshold of £20,000 per QALY gained. Assuming that there are no discontinuations (either due to loss of response or TEAEs) has the biggest impact on the ICER, with an ICER of £86,669 per QALY gained for pitolisant.

6.3 Conclusions of the cost effectiveness section

The ERG base case and scenario analyses show solriamfetol to be cost-effective in comparison to pitolisant and sodium oxybate when a threshold of £20,000 per QALY is considered. We note that when dexamfetamine and methylphenidate are included in cost-effectiveness analysis solriamfetol is not cost-effective at the £20,000 per QALY threshold. However, comparative clinical effectiveness evidence is lacking for dexamfetamine and methylphenidate.

7 END OF LIFE

The company state in the CS that solriamfetol is not a life-extending treatment and does not qualify for any end-of-life criteria. The ERG concur with this statement.

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9 APPENDICES

Appendix 1 TONES 5

Tones 5 enrolled patients from four of the company's studies of solriamfetol in patients with narcolepsy (TONES 2; TONES 1; ADX-N05 201; 15-005) and from three of the company's studies of solriamfetol in patients with obstructive sleep apnoea.

Narcolepsy populations				
Parent study	**Safety**	**Randomized into withdrawal phase**	**mITT**	**Per-protocol**
Group A (40 weeks) [a]				
Tones 2	[redacted]	[redacted]	[redacted]	[redacted]
Group B (52 weeks) [b]				
Tones 1	[redacted]	[redacted]	[redacted]	[redacted]
ADX-N05 201	[redacted]	[redacted]	[redacted]	[redacted]
15-005	[redacted]	[redacted]	[redacted]	[redacted]
Sub-total narcolepsy	[redacted]	[redacted]	[redacted]	[redacted]
OSA populations				
Parent study	**Safety**	**Randomized into withdrawal phase**	**mITT**	**Per-protocol**
Group A (40 weeks) [a]				
Tones 3	[redacted]	[redacted]	[redacted]	[redacted]
Group B (52 weeks) [b]				
Tones 4	[redacted]	[redacted]	[redacted]	[redacted]
15-004	[redacted]	[redacted]	[redacted]	[redacted]
Sub-total OSA	[redacted]	[redacted]	[redacted]	[redacted]
TONES 5 overall total	[redacted]	[redacted]	[redacted]	[redacted]

Source: Response to clarification question A4

[a] Group A were immediately enrolled in TONES 5 after completion of the parent study, there was no break in treatment

[b] Group B may have had a break in treatment between completing the parent study and enrolment in TONES 5

Appendix 2 Summary of participant characteristics in the trials included in the ERG's NMA

	TONES 2			TONES 1		Dauvilliers			Szakacs		Harmony Ibis			Xyrem, 2002				Xyrem, 2005				Black	
T'ment arm	PBO	Sol 75 mg	Sol 150 mg	PBO	Sol 150 / 300 mg	PBO	PIT 5-40 mg	MOD 100-400 mg	PBO	PIT 5-40 mg	PBO	PIT 5-20 mg	MOD 100-400 mg	PBO	SOxy 3 g	SOxy 6 g	SOxy9 g	PBO	SOxy 4.5 g	SOxy 6 g	SOxy 9 g	PBO	SOxy 6-9
N	59	59	59	49	44	30	31	33	51	54	33	67	66	34	34	33	35	59	64	58	47	55	50
Cataplexy, %	49	53	51	33	39	80	81	82	100	100	75 to 81			100	100	100	100	100	100	100	100	58	28
Age, mean, y	36	37	38	37	41	NR	NR	NR	NR	NR	40			41	44			41	42	39	40	41	35
Age, median, y	32	36	38	32	40	40	33	40	39	34	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Males, %	41	37	29	39	32	43	65	55	53	48	47			35	44	29	33	38	40	44	52	51	46
ESS, mean	17	17	17	17	17	19	18	19	17	17	18	18	18	19	NR	NR	NR	17	18	18	18	NR	NR
ESS, median	17	18	17	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	19	17	18	17	18	18	19	19	16	15
MWT20	5.6	7.1	7.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	9.7	11.3
MWT40	6.2	7.5	7.9	5.7	5.7	8.4	7.4	8.8	4.1	3.5	NR	NR	NR	NR	NR	NR	NR	9.5	8.5	9.0	7.6	NR	NR

Source: CS Table 17 and Table 18 (with any errors identified corrected) and the EPAR for pitolisant.
Abbreviations: BMI, body mass index; ESS, Epworth Sleepiness Scale; MWT20, 20 minute Maintenance of Wakefulness Test; MWT40, 40 minute Maintenance of Wakefulness Test; NR, not reported; qd, once daily; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

Appendix 3 Health-related Quality of Life Measures used in TONES 2 and TONES 5

Outcome measure	Outcome definition
FOSQ-10	• The FOSQ-10, is a 10-item disease specific QoL questionnaire to assess the effect of disorders of excessive sleepiness on functional status.[78] • Functional status is assessed through 5 subscales (activity level, general productivity, social outcome, intimacy and sexual relationships, and vigilance) and a total score.[78] • FOSQ-10 has been shown to perform similarly to the original 30-item version, exhibiting high internal consistency, effect sizes, and pre- and post-treatment differences that are highly correlated with the original 30-item version.[78] • Higher scores represent better functional status.
SF-36v2	• The SF-36v2 is a generic measure of health status with 36 questions that measures eight multi-item dimensions of health: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality (energy/fatigue), pain, and general health perception.[79] • The tool yields scores for each dimension (0–100), with higher scores representing better health, as well as two summary scores (Physical Component Summary and Mental Component Summary).[79]
EQ-5D-5L	• The EQ-5D-5L is a generic measure of health status consisting of five questions/dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) with five response levels each (no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to do).[80] • Responses are used to derive an overall EQ-5D-5L index score (0=death, 1=perfect health), and a health status VAS between 0 (“the worst health you can imagine”) and 100 (“the best health you can imagine”).[80]
WPAI:SHP	• The WPAI:SHP questionnaire is a 6-item patient-reported questionnaire that measures % of work time missed (absenteeism), % impairment while working (presenteeism), % of overall work impairment (work impairment), and % of activity impairment (activity impairment) because of a specified health problem during the past 7 days.[81,82] • The validity of the WPAI has been established in a number of diseases.[83]

	• Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.[81] A negative change from baseline represents improvement. • **TONES 2:** The WPAI:SHP was used with “narcolepsy” as the SHP. • **TONES 5**:The WPAI:SHP was used with “narcolepsy” or “OSA” as the SHP.

Source: adapted from CS Table 6

Appendix 4 Summary of risk of bias and quality assessments for comparator trials included in the ITC

Assessment Criteria	Dauvilliers 2013		Szakacs 2017		Xyrem 2002		Xyrem 2005		Black 2006		HARMONY IBIS	
	CS	ERG	CS	ERG	CS	ERG	CS	ERG	CS	ERG	CS	ERG
Was randomisation method adequate?	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Unc	Unc	Unc	NR	Yes
Was allocation adequately concealed?	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Unc	Unc	Unc	NR	Yes
Were groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Unc	Unc	Yes	Unc	Yes	Yes	NR	Yes
Were care providers, participants, and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes	NR	Yes
Were there unexpected imbalances in drop-outs between groups?	No	No	Unc	Yes	Unc	Unc	Unc	Unc	Unc	Unc	NR	No
Is there evidence to suggest that the authors measured more outcomes than they reported?	No	Unc	No	Unc	Unc	Unc	Unc	Unc	No	Unc	NR	Unc
Did the analysis include an intention-to-treat analysis?	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Unc	Yes	No	NR	Yes
If ITT conducted, was this appropriate and were appropriate methods used to account for missing data	NR	Yes	NR	Unc	NR	Unc	NR	Unc	NR	Unc.	NR	Unc
Are conflicts of interest reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	No
Were concomitant therapies aside from the trial drug(s) allowed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes
Does treatment administration reflect recommended clinical practice (i.e., initial dose and titration)?	Yes	Yes[a]	Yes	Yes	No	No	Yes	Yes	No	No	NR	No

NR: not reported in CS; Unc: Unclear

[a] Yes for pitolisant. For modafinil, dosing started with a lower dose (100 mg) than the recommended 200 mg starting dose.

Appendix 5 Errors and inconsistencies in CS NMA data inputs

The errors and inconsistencies identified by the ERG during their check of the data inputs to the key NMA that informs the health economic model (ESS 8-weeks) were:

- TONES 2: values for the numbers of patients in each group were not the mITT values
- Dauvilliers: the numbers of patients in each group are the per-protocol population but the published paper is clear that their results are based on the ITT population. As the SE is calculated from the reported SD and N for each group this automatically renders the calculated SE incorrect.
- Szakacs: SE values for the placebo arm were imputed as a weighted average of the SEs for the placebo groups reported by TONES 2 and Dauvilliers. However, due to the data extraction errors for TONES 2 and Dauvilliers, these imputed SE values are not correct. SE values for the pitolisant arm were imputed as a weighted average of the SEs for the placebo and experimental groups of the TONES 2 and Dauvilliers studies. No rationale for including the SEs of the known placebo arms in this calculation is given. Due to the data extraction errors for the TONES 2 and Dauvilliers trials these imputed SE values are also not correct.
- Xyrem 2005: The numbers in each group are not the ITT values and again, SE values are imputed based on incorrect data from the TONES 2 and Dauvilliers data extractions.
- Black 2006: The numbers of patients in each group are not the ITT values and SE values are imputed based on incorrect data from the TONES 2 and Dauvilliers data extractions.

The ERG also identified that certain of the imputation calculations provided by the Company in response to clarification question A19 appear to be incorrect. As several errors had been identified in the key 8-week ESS NMA the ERG also checked the input data for the incidence of serious TEAEs NMA and for the incidence of discontinuation due to TEAEs NMA (data presented in CS Appendix D Table 16) because the ERG planned to use these to inform the ERGs base case. In these NMAs we identified that when a continuity correction for zero events was required, this appeared to have been made incorrectly because it has only been applied to the arms with zero events and not to all arms in a trial (to maintain the relative effects).[84] Additionally, the company had not been consistent in their choice of denominators for trial arms, using a mix of denominators from either the ITT or safety populations. The ERG believes that numbers in each arm should be based on the safety population if these data are available. For the incidence of serious TEAEs the ERG found that Szakacs et al.

report there were no serious AEs and hence this study should not be included in the network. Furthermore, there is evidence that the use of the risk difference scale (which does not require a continuity correction) is inappropriate when events are rare.[85]

Appendix 6 ERG NMA data inputs

ERG corrected ESS-8 week NMA input data

STUDY	ARM	N (ITT)	SD	ESS mean change	SE	NOTES
TONES 2	Placebo	58		-2.1	0.63	
	Solriamfetol 75 mg	59		-3.4	0.64	
	Solriamfetol 150 mg	55		-5.2	0.64	
Dauvilliers 2013	Placebo	30	4.2	-3.4	0.767	SE calculated from N and SD
	Pitolisant ≤40 mg	31	6.2	-5.8	1.114	SE calculated from N and SD
	Modafinil	33	6.2	-6.9	1.079	SE calculated from N and SD
Szakacs 2017	Placebo	51		-1.9	0.569	SE calculated from mean difference
	Pitolisant ≤40 mg	54		-5.4	0.553	SE calculated from mean difference
Xyrem 2005	Placebo	59		-0.5	0.703	SE imputed as weighted average of known placebo arm SEs
	Sodium oxybate 4.5 g	64		-1	0.710	SE imputed as weighted average of known active arm SEs
	Sodium oxybate 6 g	58		-2	0.710	
	Sodium oxybate 9 g	47		-5	0.710	
Black 2006	Placebo	55		0	0.703	SE imputed as weighted average of known placebo arm SEs
	Sodium oxybate 9 g	50		-3	0.710	SE imputed as weighted average of known active arm SEs
HARMONY Ibis	Placebo	32	5.6	-3.6	0.990	SE calculated from N and SD
	Pitolisant ≤40 mg	66	4.6	-4.6	0.566	SE calculated from N and SD
	Modafinil	65	5.9	-7.8	0.732	SE calculated from N and SD

ERG corrected Serious TEAE NMA input data

STUDY	ARM	N (Safety)	Events	Notes
TONES 2	Placebo	59	0	
	Solriamfetol 75 mg	59	0	
	Solriamfetol	59	1	

	150 mg			
Dauvilliers 2013	Placebo	30	2	
	Pitolisant ≤40 mg	31	2	
Xyrem 2005	Placebo	60	0	
	Sodium oxybate 4.5 g	68	1	
	Sodium oxybate 6 g	63	1	
	Sodium oxybate 9 g	55	1	

ERG corrected Discontinuations due to TEAE NMA input data

STUDY	ARM	N (Safety)	Events	NOTES
TONES 2	Placebo	59	1	
	Solriamfetol 75 mg	59	1	
	Solriamfetol 150 mg	59	3	
Dauvilliers 2013	Placebo	30	2	
	Pitolisant ≤40 mg	31	0	
Szakacs 2017	Placebo	51	0	
	Pitolisant ≤40 mg	54	1	
Xyrem 2005	Placebo	60	1	
	Sodium oxybate 4.5 g	68	1	
	Sodium oxybate 6 g	63	4	
	Sodium oxybate 9 g	55	15	
Black 2006	Placebo	56	1	Safety Ns from Table 5 in the published paper
	Sodium oxybate 9 g	55	4	

Appendix 7 ERG Validation of company NMAs

Results obtained by the ERG that differed by 0.1 to those reported by the company are in bold in the two tables below. The remaining relative treatment effects were generally consistent (differences <0.05).

ERG analysis 1: ESS week 8 relative effects (as mean difference)

Relative effects of solriamfetol 150 mg compared to treatment	Fixed Effects		Random Effects	
	Mean	95% CrI	Mean	95% CrI
Company submission				
Placebo	-3.098	(-4.761, -1.44)	-3.107	(-7.589, 1.365)
Solriamfetol 75 mg	-1.797	(-3.456, -0.137)	-1.798	(-6.272, 2.719)
Pitolisant ≤40 mg	0.050	(-2.279, 2.377)	-0.038	(-5.704, 5.47)
Sodium Oxybate 4.5 g	-2.946	(-5.448, -0.447)	-2.974	(-9.222, 3.226)
Sodium Oxybate 6 g	-1.946	(-4.451, 0.558)	-1.965	(-8.251, 4.236)

Relative effects of solriamfetol 150 mg compared to treatment	Fixed Effects		Random Effects	
	Mean	95% CrI	Mean	95% CrI
Sodium Oxybate 9 g	0.656	(-1.518, 2.823)	0.646	(-4.892, 6.175)
ERG				
Placebo	-3.104	(-4.862, -1.345)	-3.108	(-7.684, 1.477)
Solriamfetol 75 mg	-1.779	(-3.575, -0.023)	-1.8	(-6.387, 2.777)
Pitolisant ≤40 mg	**0.155**	(-2.073, 2.374)	-0.004	(-5.767, 5.567)
Sodium Oxybate 4.5 g	-2.939	(-5.219, -0.652)	-2.971	(-9.184, 3.268)
Sodium Oxybate 6 g	-1.939	(-4.228, 0.35)	-1.978	(-8.212, 4.253)
Sodium Oxybate 9 g	0.648	(-1.418, 2.715)	0.638	(-4.916, 6.221)

Abbreviations: CrI, credible interval; ESS, Epworth Sleepiness Scale; SD, standard deviation.
A negative relative treatment effect represents an improvement (reduction) in ESS for solriamfetol 150 mg relative to the comparator.

ERG analysis 2: ESS week 12 relative effects (as mean difference)

Relative Effects of Solriamfetol 150 mg Compared to Treatment	Fixed Effects		Random Effects	
	Mean	95% CrI	Mean	95% CrI
Company submission				
Placebo	-3.797	(-5.612, -1.986)	-3.8	(-8.462, 0.789)
Solriamfetol 75 mg	-1.596	(-3.437, 0.242)	-1.593	(-6.24, 3.022)
Pitolisant ≤40 mg	-0.656	(-3.107, 1.788)	-0.741	(-6.585, 4.931)
Sodium Oxybate 4.5 g	-3.646	(-6.276, -1.017)	-3.673	(-10.04, 2.66)
Sodium Oxybate 6 g	-2.647	(-5.276, -0.023)	-2.671	(-9.05, 3.674)
Sodium Oxybate 9 g	-0.044	(-2.347, 2.262)	-0.047	(-5.724, 5.63)
ERG				
Placebo	-3.804	(-5.617, -1.99)	-3.801	(-8.379, 0.760)
Solriamfetol 75 mg	-1.599	(-3.444, 0.246)	-1.606	(-6.19, 2.966)
Pitolisant ≤40 mg	**-0.545**	(-2.816, 1.718)	-0.694	(-6.57, 4.85)
Sodium Oxybate 4.5 g	-3.639	(-5.962, -1.311)	-3.665	(-9.888, 2.512)
Sodium Oxybate 6 g	-2.639	(-4.971, -0.308)	-2.663	(-8.89, 3.547)
Sodium Oxybate 9 g	-0.052	(-2.164, 2.062)	-0.054	(-5.618, 5.52)

Abbreviations: CrI, credible interval; ESS, Epworth Sleepiness Scale; SD, standard deviation.
A negative relative treatment effect represents an improvement (reduction) in ESS for solriamfetol 150 mg relative to the comparator.

Appendix 8 Split pitolisant doses in NMA

This appendix presents a scenario analysis for the ERG's ESS 8-week NMA in which the pitolisant dose used in the Harmony Ibis trial (<20 mg) was not pooled with pitolisant doses used in the Dauvilliers and Szakacs trials (<40 mg) (**Figure 2**).

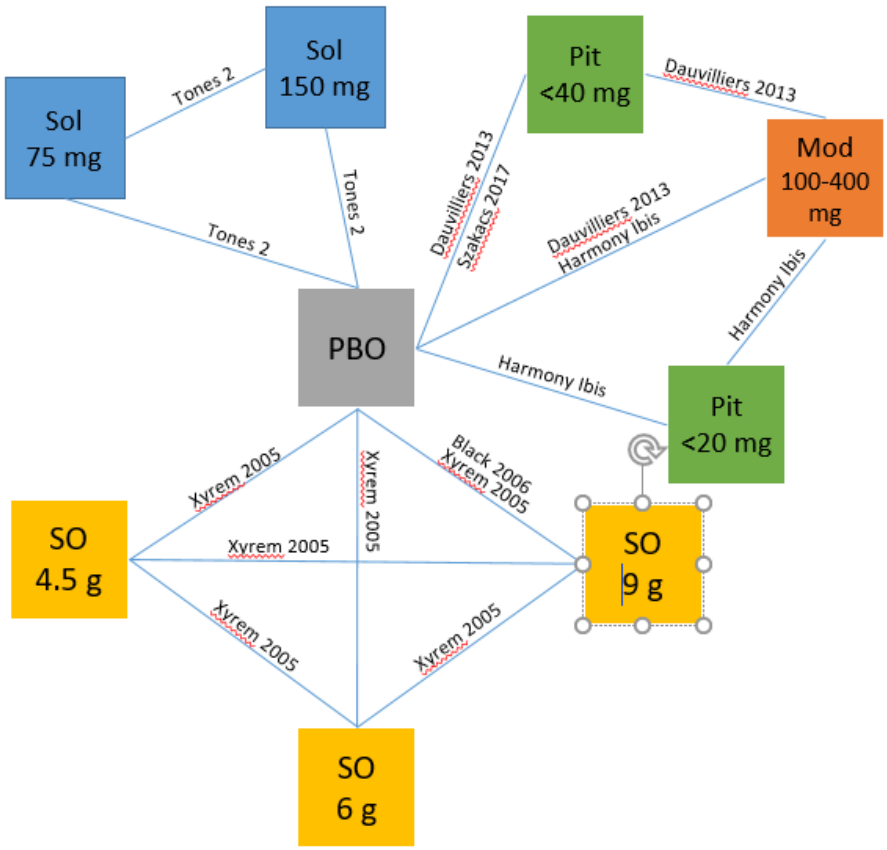

Figure 12 ESS 8-week NMA scenario: impact of separating pitolisant doses

The results of this analysis for the 8-week ESS network are shown below in Table 43. Model fit, estimated using the DIC, for the fixed-effect model (8-week ESS) was 49.797 and for the random effects model was 51.263. Given the non-meaningful difference in the DIC we prefer to use the results of the random effects model because there is some clinical heterogeneity between studies. In the ERG base case NMA, the mean relative effect of solriamfetol compared to the pooled pitolisant dose (random effects) was -0.714 (95% CrI -5.224 to 3.671). When the pitolisant doses are separated the mean results are less favourable in comparison to solriamfetol 150 mg for the ≤20 mg pitolisant dose (random effects mean -2.222, 95% CrI -7.195 to 2.762) and more favourable to the ≤40 mg pitolisant dose (random effects mean 0.045, 95% CrI -4.444 to 4.367), although there is considerable uncertainty around these estimates. The additional loop created by the splitting of the pitolisant doses did not give rise to inconsistency in the network.

Table 43 ESS week 8 relative effects (as mean difference) and absolute effects

Relative effects of solriamfetol 150 mg compared to treatment	Fixed Effects		Random Effects	
	Mean	95% CrI	Mean	95% CrI
ESS 8 week (separate pitolisant doses)				
Placebo	-3.098	-4.861, -1.331	-3.097	-6.665, 0.476
Solriamfetol 75 mg	-1.801	-3.575, -0.026	-1.801	-5.389, 1.79
Pitolisant ≤20 mg	-2.237	-4.872, 0.386	-2.222	-7.195, 2.762
Pitolisant ≤40 mg	0.141	-2.065, 2.347	0.045	-4.444, 4.367
Sodium Oxybate 4.5 g	-2.966	-5.509, -0.423	-2.972	-7.9, 1.971
Sodium Oxybate 6 g	-1.968	-4.509, 0.571	-1.968	-6.895, 2.96
Sodium Oxybate 9 g	0.654	-1.582, 2.892	0.658	-3.752, 5.049

Abbreviations: CrI, credible interval; ESS, Epworth Sleepiness Scale; SD, standard deviation.
Anegative relative treatment effect represents an improvement (reduction) in ESS for solriamfetol 150 mg relative to the comparator.

Appendix 9 Characteristics of treatments and unit costs

Table 44 Mechanisms of action and dosage

Treatment	Description[a]	Mechanism of action[a]	Dosage
Solriamfetol	DAT and NET inhibitor	Inhibits DA and NE reuptake	The recommended starting dose is 75 mg once daily. If clinically indicated in patients with more severe levels of sleepiness, a starting dose of 150 mg may be considered. Depending on clinical response, the 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 once daily.(SmPC[3])
Pitolisant	H3-receptor antagonist/inverse agonist	Increases histamine synthesis and release	The treatment should be used at the lowest effective dose, depending on individual patient response and tolerance, according to an up-titration scheme, without exceeding the dose of 36 mg/day:

			- Week 1: initial dose of 9 mg (two 4.5 mg tablets) per day. - Week 2: the dose may be increased to 18 mg (one 18 mg tablet) per day or decreased to 4.5 mg (one 4.5 mg tablet) per day. - Week 3: the dose may be increased to 36 mg (two 18 mg tablets) per day. At any time the dose can be decreased (down to 4.5 mg per day) or increased (up to 36 mg per day) according to the physician assessment and the patient's response. As long-term efficacy data are limited, the continued efficacy of treatment should be regularly evaluated by the physician. (SmPC[72])
Sodium oxybate	The sodium salt of GHB (a GABA metabolite)	Thought to act via gamma-aminobutyric acid (GABA) receptors	The recommended starting dose is 4.5 g per day. The dose should be titrated to effect based on efficacy and tolerability up to a maximum of 9 g per day by adjusting up or down in dose increments of 1.5 g/day (i.e. 0.75 g/dose). A minimum of one to two weeks is recommended between dose increments. The dose of 9 g/day should not be exceeded due to the possible occurrence of severe symptoms at doses of 18 g/day or above. Single doses of 4.5 g should not be given unless the patient has been titrated previously to that dose level.(SmPC[86])
Amphetamines (including dexamfetamine)	DAT inhibitors DAT-mediated reverse transport	Inhibits DA reuptake, increase DA release	The usual starting dose of dexamfetamine sulfate in adults with narcolepsy is 10 mg a day; dosage may be increased, if necessary, by 10 mg a day at weekly intervals to a suggested maximum of 60 mg a day (SmPC[87]).

Methylphenidate	DAT inhibitor	Inhibits DA reuptake	The recommended starting dose of methylphenidate is 10 mg a day and dosage may be increased if necessary, by 10 mg a day at weekly intervals to a suggested maximum of 60 mg a day (see European Federation of Neurological Societies [EFNS] recommendations on methylphenidate dosing [50]).

DA dopamine, DAT dopamine transporter, GABA gamma-aminobutyric acid, GHB gamma-hydroxybutyrate, NE norepinephrine, NET norepinephrine transporter

[a] based on Thorpy and Bogan 2020[55])

Table 45 Drug acquisition costs used in the company's base case analysis

Regimen	Drug	Tablets per pack	Pack price (£)	Cost per tablet (£)	Daily dose (mg)	Cost per day (£)
Solriamfetol	75 mg tablet	28	177.52	6.34	75	6.34
	150 mg tablet	28	248.64	8.88	150	8.88
Pitolisant [88]	4.5 mg tablet	30	310.00	10.33	4.5 9	10.33 20.66
	18 mg tablet	30	310.00	10.33	18 36	10.33 20.66
Sodium oxybate [89]	500 mg/ml	180 ml	360.00	0.004*	4,500 6,000 9,000	18.00 24.00 36.00

Source: reproduced from CS Table 44

* price per mg, equivalent to £4.00 per gram

Table 46 Pitolisant titration, maintenance dosing and costs assumed in the company's model

	Daily dose	Price per day	Proportion of patients	Average price per week
Titration				
Week 1	9 mg	£20.67	100%	£144.67
Week 2	18 mg	£10.33	100%	£72.33
Weeks 3–8	18 mg	£10.33	33%	£24.11
	36 mg	£20.67	67%	£96.44

	Daily dose	Price per day	Proportion of patients	Average price per week
Total cost by week 8				£1,181.44
Maintenance				
Week 8+	18 mg	£10.33	33%	£24.11
	36 mg	£20.67	67%	£96.44
Total cost per week				£120.56

Source: reproduced from CS Table 45

Table 47 Drug acquisition costs used in the company's sensitivity analysis for dexamfetamine

Regimen	Drug	Tablets per pack	Pack price (£)	Cost per tablet (£)	Cost per mg (£)
Dexamfetamine*	5 mg	28	24.70	0.88	0.18
	10 mg	30	39.78	1.33	0.13
	20 mg	30	79.56	2.65	0.13

Source: reproduced from CS Table 74

Table 48 Drug acquisition costs used in the company's sensitivity analysis for methylphenidate

Regimen	Drug	Tablets per pack	Pack price (£)	Cost per tablet (£)
Methylphenidate: Modified release capsules: Medikinet XL	5 mg	30	24.04	0.80
	40 mg	30	57.52[a]	1.92
	50 mg	30	62.52	2.08
	60 mg	30	67.32	2.24
Methylphenidate: Modified release capsules: Equasym XL	10 mg	30	25.00	0.83
	20 mg	30	30.00	1.00
	30 mg	30	35.00	1.17
Methylphenidate: Modified release tablets Concerta XL	18 mg	30	31.19	1.04
	27 mg	30	36.81	1.23
	36 mg	30	42.45	1.42
	54 mg	30	36.80	1.23

Source: reproduced from CS Table 78
[a] The unit cost in the source (the Drug Tariff[70] is £57.72.
Note: all prices are from the Drug Tariff[70]

Appendix 10 Resource use reported in TONES 5

Table 49

Table 50

Table 51

Table 52

Table 53

[redacted] **The costs incurred in different treatment arms based on the resource utilisation shown in Table 49 - Table 53 are presented in Table 54.** [redacted] **Table 54** [redacted]

[redacted] **Table 55**

[redacted]

Appendix 11 ERG model checks

ERG checks on model	*Priority*	*OK?*	*Comments*
Face validity *Are the results logical and clinically plausible?*			
The same discontinuation rates due to lack of efficacy and TEAEs have been assumed for all drugs. This is unlikely to be the case as the CS acknowledges that	Medium	?	To confirm with experts and possibly perform scenario analysis if

ERG checks on model		*Priority*	*OK?*	*Comments*
the effects on blood pressure and HR were dose dependent for Solfiamfetol.				alternative data is available.
For non-responders, model does not use IPD data on change in ESS but assumes a mean change of zero. This assumotion also has implications on the estimation of utilities.		High	No	IPD data should be used to estimate change in ESS for non-responders, just like was done for responders.
White box	*Manual checks of formulae and VBA*			
Company's implemention of bootstraping	check method	High	No	The company's bootstrap method consist of two steps. First they draw 5,000 bootstrap samples from the IPD data of 54 patients. In the their final step, they then draw 1,000 random samples from the 5,000 'bootstrap' samples. The bootstrap smaples should match the cohort size of the relevant IPD data, i.e, 54 and not 5000 for the base case.
Company's estimation of standard errors and confidence intervals for results of their bootstrap basr case and PSA results.	check formulas	High	No	Error in calculation; wrong range of cells selected in spread sheets.
Results of compandy's deterministic (univariate analysis).	Check excel formulas and VBA macros	High	No	Model VBA macro and excel formulas seem okay however results solriamfetol versus pitolisantare not reproducible as per what is report in CS. We have asked company to clarify this issue.
Results for company's threshold analysis	Check excel formulas and VBA macros	High	No	Similar issue as above.
Estimation of drug costs	Check excel formulas	High	Yes	formulas are okay
Regression formulas for utility	Check excel formulas	High	Yes	formulas are okay
Markov traces for all treatments	Check excel formulas	High	Yes	formulas are okay
Titration formulas for cost	Check excel formulas	High	?	Company's base case assumes titration for Solriamfetol 150 mg. This is based on giving

ERG checks on model	*Priority*	*OK?*	*Comments*
			sol 75 mg for the first 3 days and this represents the recommended dosing stated in the CS page 12. However, market share of 50% for both doses allows for double counting?
Black box *Change input parameters and check results are plausible - from Tech-VAR*			
Does the technology acquisition cost increase with higher prices / higher body weight / BSA?	Medium	Yes	
Does the probability of an event, derived from an OR/HR/RR and baseline probability, increase with higher OR/RR/HR?	Medium	Yes	An increase in the response rate resulted in an increase in the proprotion of patients remaining in the response state.
In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?			
For the treatment effect inputs (if from WINBUGS), are the OR, HR and RR values within plausible ranges?			
Do the sum of the number of patients in each health state sum to the cohort size?	Medium	Yes	
Check if all probabilities and number of patients in a state are equal or greater than 0.	Medium	Yes	
Check if all probabilites are less than or equal to 1.	Medium	Yes	
Check number of dead (or other absorbing state) patients is greater or equal to previous periods?	Medium	Yes	
If lifetime horizon, check if all patients are dead at end of time horizon.	Medium	Yes	
Set all utilities to 1, QALYs same as life years?	Medium	Yes	Yes. To do this, set the constants in the two mapping equations to equal 1 and set other coefficients to equal 0.
Set all utilities to 0, QALYs are zero?	Medium	Yes	Correct, set constants in the two mapping equations to equal 0.
Decrease utilities for health states, total QALYs decrease?	Medium	Yes	
Set all costs to £0, total costs are zero?	Medium	No	Cost formula for non-responders seems incorrect beyond year 1 (response rate is included in the formula in a way that adds to the cost).
Put mortality rates to 0, patients never die?	Medium	Yes	
Put mortality rates to extremely high, patients die in the first few cycles?	Medium	Yes	
Put effectiveness, utility and safety related inputs equal for all treatments, same life-years and QALYs for all treatments?	Medium	Yes	
Also set cost reltaed inputs for all treatment options equal, are costs for all treatments the same?	Medium	Yes	

ERG checks on model	*Priority*	*OK?*	*Comments*
Change around the effectiveness, utility and safety related inputs for two treatments, are life-years and QALYs reversed?	Medium	Yes	
Are the number of patients alive at any cycle lower or equal to the general population estimate?	Medium	Yes	
Are the utility estimates equal or lower than for the general population?			
Increase treatment acquisition costs, do total costs increase?	Medium	Yes	
Are incremental life years and QALYs plausible, given clinical effectiveness?	Medium	Yes	
Are incremental cost results plausible, given treatment costs?	Medium	Yes	
Total life years greater than total QALYs?	Medium	Yes	
Undiscounted results greater than discounted results?	Medium	Yes	
Divide undiscounted QALYS by undiscounted life years, is answer between minimum and maximum utility values?	Medium	Yes	
Subgroup analyses, do outcomes change if characteristics of the baseline change/	Medium	Yes	
Do life years and QALYs decrease with a shorter time horizon?	Medium	Yes	
Are the reported ICERs in the fully incremental analysis non decreasing?	Medium	?	
Do disentangled results (if reported) add up to total results?	Medium	Yes	
Is half cycle correction implemented correctly?	Medium	Yes	
Set discount rate to 0, are discounted and undiscounted results the same?	Medium	Yes	
Set discount rate to a higher values, do discounted results decrease?	Medium	Yes	
Set discount rate to extremely high value, are results similar to those in the first cycles?	Medium	Yes	
Set adverse events to 0 and then to high value, do results vary in plausible way?	Medium	Yes	
Double the difference in efficacy between the new intervention and the comparator, are results plausible?	Medium	Yes	
Half the difference in efficacy between the new intervention and the comparator, are results plausible?	Medium	Yes	
Are all necessary parameters included in the OWSA?	Medium	Yes	
Are ranges in OWSA based on confidence intervals of the parameters?	Medium	Yes	
Are results ICERs, incremental costs, QALYS for upper and lower bounds of parameters plausible and in line with expectations?	Medium	Yes	
Have the appropriate distributions been used for the parameters in the PSA?	Medium	Yes	
Check PSA output mean costs, QALYs and ICER compared to deterministic results - are they simllar?	Medium	?	A difference of £10,000 for ICEr of sol 150 mg even thopugh the cost-effectiveness implications remain the same.
Do two runs of the PSA produce similar results?	Medium	?	It takes aabout 1 hour 30 minutes to run and comes up with errors

ERG checks on model	*Priority*	*OK?*	*Comments*
Is the CEAC in line with scatterplots and efficiency frontier?	Medium	Yes	
Does the PSA scatterplot have an expected behaviour?	Medium	Yes	
Is the sum of all CEAC lines equal to 1 for WTP values?			
Are scenario analysis results plausible and in line with expectations?	Medium	?	Currently, the company's model does not perform scenario analysis. We have flagged this in clarification questions.
Do explored analyses provide a balanced view on the structure uncertainty?	Medium	?	
Are there any scenario analyses that should have been included but haven't been?	Medium	?	