NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Jazz Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Association of British Neurologists
      Sofia Eriksson, Consultant Neurologist – clinical expert, nominated by the Association of British Neurologists, authored and endorses the submission.

4. **Expert personal perspectives** from:
   a. Dr Martin B Allen, Consultant Physician – clinical expert, nominated by University Hospital North Midlands

5. **Evidence Review Group report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

6. **Evidence Review Group report – factual accuracy check**

7. **Technical Report**

8. **Technical engagement response** from **Jazz Pharmaceuticals**

9. **Technical engagement response from consultees and commentators:**
   a. Association of British Neurologists
      Sofia Eriksson, Consultant Neurologist – clinical expert, nominated by the Association of British Neurologists, authored and endorses the response.

10. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre (SHTAC)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND

Single technology appraisal

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

Document B

Company evidence submission

January 2020

File name	Version	Contains confidential information	Date
ID1602 Solriamfetol FormB_Redacted_26Nov	**2.0**	**Yes**	**26th November 2020**

Contents

Tables and figures

Abbreviations

AASM	American Academy of Sleep Medicine
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CCG	Clinical Commissioning Group
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CGI-c	Clinical Global Impression of change
CGI-s	Clinical Global Impression of severity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CM	Conservative management
CPAP	Continuous positive airway pressure
CrI	Credible interval
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CVE	Cardiovascular event
Dbar	Posterior mean of the deviance
DIC	Deviance Information Criterion
DNRI	Dopamine and norepinephrine reuptake inhibitor
DSM	Diagnostic and Statistical Manual of Mental Disorders
DVLA	Driving and Vehicle Licence Authority
EDS	Excessive daytime sleepiness
EEG	Electroencephalograph
EFNS	European Federation Neurological Societies
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EQ-5D-3L	3-level EQ-5D version
EQ-5D-5L	5-level EQ-5D version
EQ-VAS	EuroQol Visual Analogue Scale
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FOSQ-10	Functional Outcomes of Sleep Questionnaire short version
GP	General practitioner
HCP	Healthcare practitioner
HR	Heart rate

HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICSD	International Classification of Sleep Disorders
IPD	Individual patient level data
IR	Immediate release
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
LY	Life year
MCS	Mental component summary
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent to treat
MMRM	Mixed effects repeated measures
MR	Modified release
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
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea hypopnoea syndrome
PCS	Physical component summary
Pd	Effective number of parameters
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 control trial
REM	Rapid eye movement
RTA	Road traffic accident
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
SMC	Scottish Medicine Consortium
SmPC	Summary of product characteristics
TA139	NICE TA139 CPAP for the treatment of OSAHS
TEAE	Treatment-emergent adverse event
TONES	Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness
TSD	Technical Support Document
WHO	World Health Organisation
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The indication for solriamfetol is:

- To improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with narcolepsy (with or without cataplexy).

This submission focuses on part of the solriamfetol indication:

- To improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy) who have failed, have a contraindication to[1], or are intolerant to modafinil.

The proposed post-modafinil positioning is restricted compared to the marketing authorisation because this position is relevant to how clinicians have advised that solriamfetol will be used in the National Health Service (NHS). Clinician advice confirms that modafinil is widely established as the first-line therapy for narcolepsy in clinical practice in the UK, and that solriamfetol would only be considered post-modafinil, or for patients in whom modafinil is contraindicated (Table 1).

The final scope for solriamfetol for treating excessive waketime sleepiness in narcolepsy was issued by the National Institute for Health and Care Excellence (NICE) in August 2019. The decision problem for this technology appraisal is an evaluation of the clinical and cost-effectiveness of solriamfetol for the treatment of EDS in patients with narcolepsy (Table 1), in the position proposed above.

Throughout this submission evidence from the literature, including guidelines and technology appraisals, has been supplemented with research from experts working in sleep services in the UK:

[1] Hypersensitivity to the active substance or to any of the excipients. Myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias and other serious heart problems. Concomitant use of monoamine oxidase inhibitors or within 14 days after MAOI treatment has been discontinued.

- Jazz Pharmaceuticals interviewed UK Healthcare Practitioners (HCPs) (n=9 respondents to 24 invitations hereafter referred to as “Sleep Services Analysis”) in June 2019 to understand the current clinical pathway for EDS associated with narcolepsy and the potential place in therapy of solriamfetol (1).
  - Respondents were Consultant Neurologists (n=3), Clinical pharmacist (n=1), Consultant Physician in Respiratory and Sleep Medicine (n=1), Sleep Centre Service Manager (n=1), Clinical Commissioning Group (CCG) Commissioning Pharmacist (n=1), and CCG Head of Medicines Management (n=2).
  - Four respondents were from the North of England, two from London/Kent, one was from the Midlands and two were from the South West.
- In order to fully understand the treatment of narcolepsy in UK clinical practice, Jazz Pharmaceuticals interviewed key opinion leaders (KOLs) in the management of narcolepsy between July and November 2019 (n=7; hereafter referred to as “KOL Clinical Practice Interviews”) (2).
  - All respondents were consultants who manage patients with narcolepsy, either in respiratory disease, sleep disorders or neurology.
  - Four respondents were from the North/North West, and three were from the South/South East.
- Within the interviews, between 3 and 6 interviewees responded to each question and the results were summarised to generate a broad picture of narcolepsy management in UK clinical practice.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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, 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.
Intervention	Solriamfetol	Solriamfetol	Solriamfetol
Comparators	• 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. • 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 is 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.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; EDS, excessive daytime sleepiness; KOL, key opinion leader; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NHS, National Health Service.

B.1.2 Description of the technology being appraised

A summary of product characteristics (SmPC) for information for use of solriamfetol in treating EDS in patients with narcolepsy is provided in Appendix C.

Solriamfetol is a wake promoting agent, intended to treat EDS by improving wakefulness and reducing EDS in patients with disorders of EDS including narcolepsy and obstructive sleep apnoea (OSA).

For treating EDS in patients with narcolepsy, solriamfetol is administered orally, once daily, at a starting dose of 75 mg and titrated to a maximum dose of 150 mg, by doubling the dose at an interval of at least 3 days.

Although studied in clinical trials (Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness [TONES] studies) the 300 mg once daily dose is not licensed for patients with narcolepsy.

Further details for solriamfetol, including the indication, regulatory status, method of administration, dosing, and related costs are provided in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	Solriamfetol (Sunosi®)
Mechanism of action	Solriamfetol is a derivative of the amino acid phenylalanine. The mechanism(s) by which solriamfetol exerts its wake-promoting effects in humans is/are yet to be fully characterised but is/are thought to be through activity as a DNRI.
Marketing authorisation/CE mark status	• A regulatory submission was made to the EMA in November 2018. • CHMP positive opinion was received on 15 November 2019 with marketing authorisation expected to be granted by the European Commission on 20th January 2020.
Indications and any restriction(s) as described in the summary of product characteristics	The indication for solriamfetol is to:† • Improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy). • Improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP. **This technology appraisal considers the EDS in narcolepsy indication only. ID1499 will consider the EDS in OSA indication.**
Method of administration and dosage	Available as 75 mg and 150 mg orally-administered film-coated tablets. • The recommended starting dose in patients with narcolepsy is 75 mg once daily, upon wakening. • 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 from 75mg 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. • The need for continued treatment and the choice of appropriate dose should be periodically assessed during extended treatment in patients prescribed solriamfetol.
Additional tests or investigations	None. Based on the Sleep Services Analysis[b] and KOL Clinical Practice Interviews, all patients with narcolepsy receive similar monitoring in terms of frequency of tests, measurements and appointments, and although the type of test required may differ slightly by treatment, these are typically conducted during routine visits. The introduction of solriamfetol is not anticipated to require any additional resource use compared with any existing treatment for EDS in narcolepsy, but is expected to require less resource use compared with dexamfetamine and methylphenidate, both of which require ongoing monitoring of psychiatric and cardiovascular status.
List price and average cost of a course of treatment	• Anticipated list price £177.52 per pack of 28 x 75 mg film-coated tablets (equating to 28 days treatment; unit price £6.34 per tablet). • Anticipated list price £248.64 per pack of 28 x 150 mg film-coated tablets (equating to 28 days treatment; unit price £8.88 per tablet).

[b] Jazz Pharmaceuticals interviewed UK Healthcare Practitioners (HCPs) (n=9 respondents to 24 invitations; referred to as "Sleep Services Analysis") in June 2019 to understand the current clinical pathway for EDS associated with narcolepsy and the potential place in therapy of solriamfetol.

	• The anticipated total cost per year of treatment at list price would be: – £2,308 at the 75 mg dose. – £3,232 at the 150 mg dose. The need for continued treatment should be periodically assessed during extended treatment in patients prescribed solriamfetol†
Patient access scheme (if applicable)	Not applicable.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CPAP, continuous positive airway pressure; DNRI, dopamine and norepinephrine reuptake inhibitor; EDS, excessive daytime sleepiness; EMA, European Medicines Agency; OSA, obstructive sleep apnoea.
† The summary of product characteristics for solriamfetol is presented in Appendix C.

B.1.3 Health condition and position of the technology in the treatment pathway

Overview of narcolepsy and associated symptoms

EDS is the defining characteristic of a group of sleep disorders known as central hypersomnia; the focus of this submission is EDS in narcolepsy, a rare and chronic form of central hypersomnia (3, 4). Narcolepsy is characterised by an inability to appropriately regulate sleep-wake cycles (5, 6), resulting in sporadic and uncontrollable occurrences of rapid eye movement (REM) sleep during wakefulness, and disrupted sleep patterns (3, 4, 7). Patients with narcolepsy consequently find it difficult to remain awake during waking hours (7) and experience EDS (chronic tiredness, similar to feeling severely sleep-deprived) (8).

The presence of EDS is an essential feature of the 3rd edition of the International Criteria for Sleep Disorders (ICSD) diagnostic criteria for narcolepsy (9), and all patients with narcolepsy suffer from EDS. Patients experience 'sleep attacks' and, despite fighting the urge to sleep, they will unintentionally fall asleep for short periods during the day (7, 10), including at inappropriate or potentially dangerous times such as during driving, cycling, eating, or mid-conversation (8). There is no cure for narcolepsy thus the associated EDS is lifelong (11, 12), and has a substantial negative impact on the patient's ability to function psychologically, socially, and professionally (4).

After EDS, cataplexy is the second most common symptom (13), affecting approximately 70% of patients with narcolepsy (14). Cataplexy causes the patient to experience a sudden, bilateral, involuntary loss of muscle tone whilst remaining conscious and can be triggered by a range of factors, including strong emotions (positive or negative) (6, 13). Cataplexy severity ranges from mild (e.g. facial weakness, buckling of the knees, weakness in the arms) to very severe (e.g. muscle paralysis), and cataplectic attacks can last from seconds to minutes (6, 14).

In addition to their inability to stay awake, patients with narcolepsy also have difficulty remaining asleep for extended periods of time (7). Approximately one-third of patients with narcolepsy experience disrupted nocturnal sleep, which impacts their social and professional life (14). One review reported patients with narcolepsy awoke

3.3–4.6 times per night and stayed awake for 31.5–41.3 minutes (compared with 1.3–1.4 times per night for 10.4–33.1 minutes for controls without narcolepsy) (15). Additional symptoms of narcolepsy include hypnagogic/hypnopompic hallucinations (dreamlike REM sleep experiences upon falling asleep/waking, respectively), sleep paralysis, or insomnia; however, these are less frequent than EDS and cataplexy (10, 16, 17) and their presence is not required for a diagnosis of narcolepsy (11).

Epidemiology of narcolepsy

Data on the incidence and prevalence of narcolepsy in the UK are extremely limited. The NHS webpage on narcolepsy and Narcolepsy UK webpage estimate that 30,000 people in the UK have narcolepsy, equating to 40 per 100,000[c] population (12, 18). This value is believed to be derived from a European[d] survey in which approximately 19,000 randomly selected members of the general population were surveyed by telephone and those that met ICSD criteria for a narcolepsy diagnosis (cataplexy and EDS) were tagged as having narcolepsy (19). Although this methodology is flawed, missing true diagnostic testing such as through sleep studies, this value is broadly consistent with other EU estimates of 25–50 per 100,000 population (20).

It is acknowledged by Narcolepsy UK that the majority of these patients will not have received a formal diagnosis for their condition (18), and thus will not be receiving treatment; per NICE Evidence Summary 8 for pitolisant (hereafter "NICE ES8") of these estimated 30,000 people with narcolepsy it is believed that around 5,000 people will have received a diagnosis and are currently being treated (3). According to the KOL Clinical Practice Interviews, once diagnosed, the majority of patients with narcolepsy will receive treatment and only a small minority (<5%) are untreated (reasons included personal choice, intolerance of side effects, or pregnancy).

For incident cases of narcolepsy, a separate European study[e] (years: 2000–2010) estimated the incidence rate for diagnosed narcolepsy in the UK to be 1.02 per

[c] Equivalent to 1 in 2,500 as quoted by Narcolepsy UK (18).

[d] Including the UK, Germany, Italy, Portugal, Spain.

[e] Including the Denmark, Finland, Italy (Tuscany and Emilia Romagna regions), the Netherlands (NL), Sweden, and the UK.

100,000 population across all age groups, with a higher incidence rate of 1.22 per 100,000 population between 5–19 years (21).

The exact cause of narcolepsy remains unknown but genetic and environmental factors (e.g. streptococcal infections, H1N1 influenza and vaccination [19]) are involved (8). Deficiency in hypocretin (orexin) has been identified as a cause of both sleep fragmentation and the disruption of the monoamine systems associated with the symptoms of narcolepsy (8). The disease does not manifest at birth, and instead, patients are commonly diagnosed during adolescence or middle age (3, 22), which supports the role for environmental factors in disease pathogenesis (8).

Patient burden of narcolepsy and EDS

Narcolepsy routinely and seriously affects patients' everyday function, while placing a substantial medical and economic burden on the patient (23); it is consequently associated with a high burden of illness. The burden of narcolepsy varies according to the patient's age at diagnosis and the delay from symptom onset to diagnosis (24). In the UK, the majority of patients with narcolepsy report problems with school, work, mood, leisure or relationships (25), demonstrating the widespread impact of their condition and its symptoms. In a Narcolepsy UK survey of patients with narcolepsy (n=302) and their carer/supporters (n=149), 88% said their narcolepsy affected the activities they do, 65-66% reported difficulties maintaining friendships or building and maintaining relationships, and 86% said their narcolepsy affected the time they spent with their friends (26).

Patients with symptom onset during childhood or adolescence are more likely to miss time at school or interrupt their education because of their condition, compared with the general population (27, 28). Children and young adults with narcolepsy have reduced quality of life (QoL) compared with non-narcoleptic controls (29). In children and young adults, the symptoms of narcolepsy impact learning, academic performance, social participation, and their ability to remember instructions. These patients may also require special education classes and/or scheduled naps to help them cope with the symptoms of their condition and perform academically (24, 29-31).

In adults, the symptoms of narcolepsy, including EDS can interfere with personal relationships, daily activities, social interactions and employment (23, 32, 33). Patients with narcolepsy are commonly considered lazy or unmotivated due to the impact of their symptoms (10), and young adults with narcolepsy (18–37 years) are more likely to report anxiety, depression, social rejection and social isolation compared with non-narcoleptic controls (33). Furthermore in a UK survey, approximately 1 in 3 patients with narcolepsy said their condition caused a relationship to end, or caused problems at home (with cooking, supervising children, or accidents) (25), and in a separate survey, 57% of patients reported that their narcolepsy had affected their children (26).

With respect to EDS in narcolepsy, EDS is the primary clinical symptom of narcolepsy and is usually the first symptom to present; EDS often has the greatest impact on daily life (34). Patients with narcolepsy experience negative impact on their employment and career compared with people without the condition, for example, people with narcolepsy who are employed are more likely to require sick leave, have a work disability, or miss work either directly due to their condition, or indirectly as a result of hospitalisation or diagnostic procedures due to their disease (27, 33). Furthermore, irresistible sleepiness (i.e. EDS) is directly associated with lost working days, and indirectly associated with high costs (27), indicating that EDS due to narcolepsy can affect a patient's career and finances. For example, in a UK cohort of patients with narcolepsy and supporters/carers, 82% found narcolepsy negatively affected the type of work they could do (26). Their ability to find (65%), progress within (76%) or keep a job (64%) was also negatively impacted (26) and approximately 30% of patients lose/leave their job due to their narcolepsy (27, 33). Perhaps because of this, only 59% of respondents to the UK survey were working, and only 54% reporting being willing to talk to employers about their diagnosis. Some careers, such as shift work or those that require driving, may be unsafe and therefore unsuitable, as the patient may require work adjustments or special arrangements (such as naps) that do not suit the demands of the work schedule and consequently interfere with their career (8). The impact of narcolepsy on work productivity can have financial implications for patients (23): young adults with

narcolepsy (18–37 years) report significantly more financial insecurity compared with non-narcoleptic controls (33).

The effects of narcolepsy can extend to the patient's family or household (35). For example, a Danish study reported that patients' partners were more likely to earn less from their employment, and have significantly higher healthcare costs ($p<0.001$), compared with the partners of non-narcoleptic controls (35). A European study reported the patient's partner/friends were negatively affected (to a lesser extent compared with the patient) by the patient's symptoms of narcolepsy including EDS, difficulty concentrating/focusing, negative impact on mood/morale, or ability to undertake physicals tasks (36). Several studies show that patients with narcolepsy have significantly lower health-related quality of life (HRQoL) compared with the general population, in particular on the vitality domain (25, 37-41). A 5-year study showed that the impact of narcolepsy on patients' HRQoL does not improve over time, consistent with the chronic nature of the disease and its symptoms (39).

Similarly, evidence from studies on patients with EDS specifically show the detrimental impact that this symptom can have on QoL, compared with people without EDS (42); given that all patients with narcolepsy have EDS by definition (9), it is thus a clear driver of HRQoL burden in these patients. Sleep disturbance is associated with depression (43), and patients with narcolepsy are almost twice as likely to report depression compared with people without narcolepsy (44). Patients with narcolepsy and depression have significantly worse QoL, compared with patients with narcolepsy and without depression (37). Respondents to the KOL Clinical Practice Interviews reported that patients highly value having their EDS managed; with KOLs using language such as 'life changing' when discussing management of EDS (2).

As narcolepsy can be difficult to diagnose, the burden to patients can persist for many years: in the UK there is an estimated median delay of 10.5 years between first symptom and diagnosis (mean: 15 years) (45). During this time, patients may receive multiple referrals and/or misdiagnoses including for depression, anxiety, disorder and insomnia (24). Therefore, after these extended periods of reduced QoL due to their undiagnosed narcolepsy, upon their (eventual) diagnosis, rapid and

effective treatment is critical to maximise the patient's QoL and improve daily function.

Healthcare burden of narcolepsy and EDS

Data on the healthcare burden of narcolepsy in the UK are limited. However, the few available studies from Europe and the USA show that narcolepsy places a substantial burden on healthcare systems and that healthcare resource utilisation is higher for patients with narcolepsy compared with the general population (23, 44).

Studies from the USA show that patients with narcolepsy have higher healthcare utilisation compared with age and gender matched non-narcolepsy controls (average annual cost 2006–2010[f]: £9,011 per patient with narcolepsy, vs. £4,051 for controls); total costs included inpatient admissions, emergency department/hospital outpatient admissions, and drug costs (46). Furthermore, patients with narcolepsy are more likely to be injured in motor vehicle and non-motor vehicle accidents (i.e., falls, and non-fall related home and work injuries); those patients with higher levels of sleepiness or a shorter time since diagnosis are at the greatest risk of accident (47). However, the healthcare burden of narcolepsy can be reduced with effective treatment. For example, a study in the USA showed that patients had a significant decrease in medical costs after receiving modafinil or armodafinil (not available in the UK), compared with before treatment (respective costs from 2009–2012[f]: £11,799 vs. £10,591 for modafinil; £10,129 vs £8,750 for armodafinil; $p<0.001$); cost components included inpatient hospitalisation, emergency department visits, physician visits, and laboratory/diagnostics claims not related to hospitalisation/any other visits (48).

Patients typically experience a long delay prior to correct diagnosis of narcolepsy, with one UK study quoting the median time from first symptoms to diagnosis of 10 years (45, 49). Many patients receive multiple referrals and/or misdiagnoses (24, 50). One USA study found that patients made an average (standard deviation [SD]) of 5.8 (10.0) physician visits before receiving a correct diagnosis (51); this pattern of

[f] Values were converted from USD to GBP at exchange rate on 21 Nov 2019 (1 USD:0.77 GBP). Inflation was not taken into account.

re-referral and misdiagnosis represents an unnecessary use of healthcare resources (including outpatient appointments, drugs, inpatient care, nursing and diagnostic procedures) and contributes substantial cost and burden to healthcare systems (51).

Guidelines for the treatment of narcolepsy and EDS

Methylphenidate and dexamfetamine were included as comparators in the final NICE scope for this appraisal and are covered in the following sections.

According to the KOL Clinical Practice Interviews, both are used to varying extents in clinical practice for patients with narcolepsy, although the licensing status across different formulations of these drugs is not consistently known by clinicians.

Methylphenidate is available in various formulations, including immediate-release (IR) and modified-release (MR) formulations. Although methylphenidate does have a marketing authorisation in attention-deficit/hyperactivity disorder, there are no formulations that have a marketing authorisation for the treatment of patients with narcolepsy.

Dexamfetamine is available in various formulations, including tablets, oral solution and MR capsules. Based on SmPCs published on the Medicines & Healthcare Regulatory Agency (MHRA) website, only the oral solution and tablets are licensed in narcolepsy. However, SmPCs are not published on the Electronic Medicines Compendium (EMC) website (https://www.medicines.org.uk/emc/).

There are no national guidelines that specifically cover the management of narcolepsy, nor the treatment of specific symptoms such as EDS in narcolepsy, in England. More broadly, the NHS webpage for narcolepsy outlines ways to manage the symptoms of narcolepsy, such as adopting good sleeping habits, receiving counselling, or taking medication to treat the symptoms (52). NICE Guideline 127 for suspected neurological conditions (NG127) recommends that adults with excessive sleepiness or narcolepsy are referred for neurological assessment, but does not make any recommendations on treatment (53).

In the absence of specific UK guidelines on the pharmacological management of narcolepsy or its symptoms, the most relevant international guidelines are those from the European Federation of Neurological Societies (EFNS) for the management of narcolepsy (2011) which recommend the following treatments for EDS in narcolepsy (11):

- Modafinil as first-line treatment when the most disturbing symptom is EDS, **or**
- Sodium oxybate, where EDS is concomitant to cataplexy and poor sleep, **or**
- Methylphenidate (unlicensed in narcolepsy) can be used:
  - Where modafinil is insufficient and sodium oxybate is not recommended, *or*
  - Where short acting effects are needed to supplement modafinil (i.e. at specific times of the day, and/or where maximum alertness is required).

The EFNS guidelines also recommend behavioural treatment measures for narcolepsy, such as regular nocturnal sleep routines, and planned naps during the day, and state that regular follow-up is necessary to monitor the patient's response to treatment and encourage the patient to persist with their treatment plan (11). However, the guidelines are significantly out-of-date and not widely recognised or used in UK clinical practice. Evidence from the Sleep Service Analysis and KOL Clinical Practice interviews (1, 2) suggests that although local guidelines and treatment algorithms sometimes exist, there is wide variation in the management of narcolepsy; modafinil is established as first-line in clinical practice, but beyond first-line therapy, there is substantial local variability in practice, depending on clinical opinion, preference, and local funding and/or guidelines.

Clinical pathway in the UK and proposed place in therapy for solriamfetol

As outlined above, national guidelines on the management of narcolepsy have not been established. Based on evidence generated from the Sleep Services Analysis and the KOL Clinical Practice Interviews, modafinil is the only treatment option with a widely established place in UK clinical practice for treating EDS due to narcolepsy, i.e. first-line (1, 2). This is consistent with a study conducted in a single sleep centre in the UK, which found that 93% of patients with narcolepsy in a UK cohort received modafinil first-line (54). The use of modafinil is supported by clinical trial data in this

indication (55, 56). However, 20–66% of patients can be unsuccessful[g] on first-line modafinil (1, 2, 54), representing a clear unmet need for subsequent treatment choices. Further, first-line modafinil may not be suitable for all patients due to contraindications, cautions and interactions.

According to the Sleep Services Analysis and KOL Clinical Practice Interviews there is no widely established second-line therapy for patients with narcolepsy. Although there are broad local variations in practice, typically, if modafinil does not significantly improve the patient's symptoms, the patient may subsequently receive any of the other available pharmaceutical-based treatments (methylphenidate, dexamfetamine, sodium oxybate, or pitolisant), and will typically cycle through treatments until they achieve a response (1, 2). A recent review by the Specialist Pharmacy Service and NHS England concluded that access to sodium oxybate was inconsistent across the UK due to funding status (57); information from the KOL Clinical Practice Interviews suggests that a similar picture exists for pitolisant (2). This is further supported by regional treatment pathways available online for two NHS Prescribing Committees (London, Merseyside) and the Northern Treatment Advisory Group (58-60).

Respondents to the KOL Clinical Practice Interviews state that modafinil is considered the first-line choice in patients for whom it is suitable. Based on this positioning, and according to additional information from the Sleep Services Analysis, solriamfetol would be considered as an option for patients in whom modafinil has failed, has not been tolerated or is contraindicated (1, 2). In these situations (i.e. subsequent to first-line modafinil) methylphenidate (unlicensed in narcolepsy), dexamfetamine, sodium oxybate or pitolisant may be considered appropriate comparators for solriamfetol.

Limitations associated with current treatments for narcolepsy

Many stimulant drugs used for the treatment of narcolepsy, including dexamfetamine, and methylphenidate (unlicensed in narcolepsy) are well known for their addictive profile (61). Furthermore, the licences for dexamfetamine,

[g] Unsuccessful defined as discontinuing modafinil (or switching treatment) for any reason including personal choice, failure to respond, loss of response over time, or side effects.

methylphenidate, and sodium oxybate contain warnings on the potential for dependence with long-term use and state that patients should be carefully monitored for signs of abuse or dependence, both during treatment and after treatment discontinuation (62-66). The licences for sodium oxybate and dexamfetamine state that withdrawal syndrome or rebound effects may occur on discontinuation; further, abrupt withdrawal of dexamfetamine can be associated with insomnia, changes in electroencephalography (EEG) during sleep, and/or extreme fatigue (63, 65), indicating that long-term treatment with dexamfetamine may modify sleep architecture. The licence for pitolisant states that preclinical studies on drug dependence and drug abuse liability did not draw any definitive conclusions on tolerance or dependence (67).

In addition to the potential dependence and withdrawal effects of these treatments, their dosing regimens may be inconvenient or incompatible with the patient's lifestyle. Dexamfetamine and methylphenidate may require the patient to take multiple doses per day or to split their dose between morning and afternoon, while sodium oxybate requires the patient to take one dose at bedtime and then wake up during the night for a second dose. These comparators may also have food/meal-related restrictions (such as pitolisant which is taken with food at breakfast) which further disrupt the normal routine of patients who already experience difficulties with their daily activities due to their narcolepsy (62-67). Furthermore, the currently available treatments are not recommended in women who are pregnant[h] or breastfeeding, with the exception of methylphenidate and pitolisant which may be prescribed if the benefits outweigh the risks of postponing treatment or to the foetus, respectively (63-68) (see Appendix C).

Fatigue caused by sleep deprivation can impair driving abilities to levels comparable or worse than that observed with drunk driving (69, 70). One study showed that 16.9–18.6 hours of sleep deprivation caused driving impairment equivalent to a blood alcohol content of 0.05%, increasing after 17.6–19.7 hours of sleep deprivation

[h] There are limited data from the use of solriamfetol in pregnancy and it is unknown whether solriamfetol is excreted into human milk. Solriamfetol is not recommended during pregnancy and in women of childbearing potential not using contraception. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from solriamfetol therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the women.

to a equivalence with a blood alcohol content of 0.1% (70). The maximum legal blood alcohol content in the UK is 0.08% (71), which indicates that for patients with narcolepsy whose condition is not well-controlled, their level of EDS may substantially impair their ability to drive and/or place them at risk of an accident. A separate study showed that people with 24 hours of sleep deprivation had worse impairment in driving ability than people who were rested but had a blood alcohol content of 0.05% (69). In the UK, patients with narcolepsy are required to inform the Driver and Vehicle Licensing Agency (DVLA) about their condition, and are only permitted to continue driving if the DVLA is satisfied that their condition is well controlled (72). However, some treatments for narcolepsy including dexamfetamine and methylphenidate, can cause blurred vision and/or dizziness which may affect driving ability (62, 63, 65, 66) – the licences for dexamfetamine and methylphenidate state that these treatments may have a moderate influence on the ability to drive and use machines (63, 64, 68). The overwhelming EDS and disruption to night-time sleep experienced by patients with narcolepsy, combined with the negative impact of current treatments on driving ability, therefore leaves patients with narcolepsy either unable to drive, or at a high risk of unsafe driving if their condition is not sufficiently controlled to drive safely.

The currently available pharmaceutical-based therapies used to treat narcolepsy have a range of clinically relevant pharmacokinetic interactions (63, 64, 66-68). For example, the licences for sodium oxybate, pitolisant and methylphenidate include warnings against the use of alcohol in conjunction with treatment. Pitolisant induces CYP3A4 and CYP2B6 at therapeutic concentrations and its use should therefore be avoided with substrates of CYP3A4 with a narrow therapeutic margin. Conversely, pitolisant metabolism is impacted by potent CYP3A4 inducers and CYP2D6 inhibitors such that dose adjustments may be required; further, antidepressants or antihistamines may impair the efficacy of pitolisant. The oral contraceptive should not be used with pitolisant, Methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants and some antidepressants such that when starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times). Dexamfetamine is impacted by a variety of

medications that either act to increase or decrease the blood levels of dexamfetamine; conversely dexamfetamine may also increase or decrease the effects of a range of medications. Both methylphenidate and dexamfetamine are contraindicated in patients receiving monoamine oxidase inhibitor treatments.

Unmet need in patients with narcolepsy

Narcolepsy is highly pervasive and can impact all aspects of the patient's life including relationships, physical health, family life, education and/or career (32, 73). Despite taking "standard treatments"[i], an estimated 70% of patients continue to experience EDS every day (European study of patients seen in specialist sleep centres, including four in the UK (36)). The severe and chronic nature of EDS due to narcolepsy is a major complaint for those suffering from narcolepsy (8), and in the UK, only 58% of patients with narcolepsy feel they currently have access to the best medications to treat their condition (26).

As described previously, modafinil is the first-line treatment for narcolepsy in the UK, however, 20–66% of patients can be unsuccessful[g] on first-line modafinil (1, 2, 54). Patients with narcolepsy who have failed, are intolerant, or have a contraindication to modafinil have limited treatment options for the long-term management of their EDS due to narcolepsy. Evidence from the KOL Clinical Practice Interviews suggests that treatment is highly individualised to each patient's needs and level of the impact of their EDS on function; furthermore, response to a given pharmaceutical-based treatment varies widely between patients (2); these findings suggest that no single treatment pathway would be suitable for all patients. There is therefore an unmet need for a well-tolerated, long-term treatment for their EDS that lasts throughout the day, and offers a dosing regimen that complements the patient's lifestyle (without affecting their mealtimes, driving ability or night-time sleeping patterns), but has low potential for abuse and dependence.

Solriamfetol is a once daily, oral treatment that offers long-term effective and well-tolerated improvements in EDS, without affecting sleep architecture, and is not

[i] Daytime medications taken during the study period were modafinil (62.7%), methylphenidate (19.4%) and antidepressants, including venlafaxine (11.9%), clomipramine (11.9%), fluoxetine (7.5%), paroxetine (4.5%) and dextroamphetamine (3.0%). Sodium oxybate was taken at night by 26.9% of the patients.

associated with dependence or withdrawal-associated rebound hypersomnia. The solriamfetol dosing regimen is less disruptive and more convenient than that of its comparators – it is a once daily, oral treatment, taken with or without food upon awakening, has negligible to minor influence on driving ability; clinically relevant pharmacokinetic drug interactions are unlikely to occur with solriamfetol (see Appendix C).

B.1.4 Equality considerations

There are no equality considerations for this submission.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Direct head-to-head comparisons of solriamfetol versus other relevant pharmacologic comparators have not been conducted in a clinical trial setting, as current Phase 3 trials compare solriamfetol to placebo. Two systematic searches were conducted to identify clinical evidence for interventions used in the treatment of EDS associated with narcolepsy, with the intention of indirectly comparing these interventions via meta-analysis.

1. **Randomised controlled trial (RCT) search:** The first search sought RCT evidence, representing the most robust evidence for inclusion in meta-analysis. This search identified 17 citations describing 13 unique trials. Of these, 11 citations describing 7 unique trials met the criteria for inclusion in an indirect treatment comparison (ITC).
2. **Additional stimulants search:** In the absence of any RCT evidence having been identified for the NICE comparators, methylphenidate and dexamfetamine, an additional search specifically for stimulant studies of any design was performed to ensure that all potentially relevant stimulant studies were identified. The purpose of this search was to allow an assessment of comparative stimulant evidence to be conducted, to allow incorporation into the ITC or potentially allow a naïve comparison. This search identified 17 citations (17 studies), none of which could be incorporated into the ITC.

The systematic literature reviews (SLRs) are described in detail in Appendix D as follows:

- RCT search strategy in Section D.1.1
- Stimulants search strategy in Section D.1.2
- Study selection covering both searches in Section D.1.3

The subsequent ITC is described further in Section B.2.9 and Appendix D (Section D.1.4 and D.1.5).

B.2.2 List of relevant clinical effectiveness evidence

The clinical trial programme for solriamfetol in narcolepsy investigated solriamfetol daily doses of 75, 150 and 300 mg. The solriamfetol 300 mg dose will not be licenced in narcolepsy but has been included where necessary to describe the trial design and baseline characteristics of the trial population. Results for the 300 mg dose have not been presented (TONES 2 and TONES 1), with the exception of TONES 5 where results are generally only available as a single, combined dose arm (75, 150 and 300 mg).

The Phase 3 clinical trial programme for solriamfetol consists of four trials (TONES 2-5) which provide evidence for the treatment of EDS in patients with narcolepsy or OSA:

- TONES 2 (14-002): 12-week, double-blind, placebo-controlled study for EDS in narcolepsy.
- TONES 3 (14-003): 12-week, double-blind, placebo-controlled study for EDS in OSA.
- TONES 4 (14-004): 6-week, double-blind, withdrawal study for EDS in OSA.
- TONES 5 (14-005): long-term, open-label extension safety and maintenance of efficacy study for EDS in narcolepsy and OSA (including a 2-week placebo-controlled, randomised-withdrawal phase after patients had completed ≥6 months of treatment with solriamfetol).

In addition, two Phase 2 trials have been conducted in patients with narcolepsy:

- ADX-N05 201: Phase 2a, 4-week, double-blind, placebo-controlled, crossover study for EDS in narcolepsy (74). Two groups were tested: (i) placebo for 2 weeks, followed by 1 week of solriamfetol 150 mg then 1 week of solriamfetol 300 mg or (ii) solriamfetol 150 mg for 1 week, followed by solriamfetol 300 mg for 1 week, then 2 weeks of placebo. ADX-N05 201 provided proof of concept and information for the design of the Phase 3 studies and demonstrated the clinical benefit and meaningful improvements achievable with solriamfetol in patients with narcolepsy. With the availability of Phase 3 data for EDS in narcolepsy and with the short-term crossover design of ADX-N05 201, this study does not provide any additional data to that considered in

Phase 3 or that could be of use in the cost-effectiveness analysis. As such this study has not been described further in this submission.

- TONES 1 (ADX-N05 202): Phase 2b, 12-week, double-blind, placebo-controlled study for EDS in narcolepsy (75). TONES 1 assessed the efficacy of 4 weeks of treatment with solriamfetol 150 mg, followed by 8 weeks with solriamfetol 300 mg, compared to placebo.

This submission is for solriamfetol for EDS in narcolepsy.

- The primary comparative data comes from the Phase 3 study TONES 2, which provides evidence across the full licensed dose range (75 mg and 150 mg) for the SmPC, and to be used in clinical practice.
- Long-term data comes from the Phase 3 study TONES 5 (which includes data from the unlicensed 300 mg dose of solriamfetol).
- TONES 1 is also included to provide comparative evidence; however, as a Phase 2 study with a smaller population and limited to sequential testing of the solriamfetol 150 mg and unlicensed 300 mg doses, it is considered as supporting evidence only.
- The three TONES studies in narcolepsy are summarised in Table 3.

The pivotal trials supporting the treatment of EDS in OSA (TONES 3 and TONES 4) will be considered in the upcoming appraisal of solriamfetol for treating EDS caused by OSA (ID1499).

Table 3. Clinical effectiveness evidence

Study (Study number)	TONES 2 (Study 14-002)	TONES 1 (Study ADX-N05 202)	TONES 5 (Study 14-005)
Data sources	**Key sources:** CSR (76); Thorpy 2019 Ann Neurology (77) **Supporting sources:** Dauvilliers 2018 (78); Emsellem 2019 (79); Rosenberg 2018 (80); Thorpy 2017 (81); Thorpy 2018 (82)	**Key Sources:** CSR (83); Ruoff 2016 Sleep (75)	**Key data sources:** CSR (84); Malhotra 2019 Sleep (85) **Supporting sources:** Weaver 2019 (86)
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, four-arm parallel-group, 12-week safety and efficacy study	Phase 2b, multicentre, randomised, double-blind, placebo controlled, two-arm parallel-group, 12-week safety and efficacy study	Phase 3, multicentre, open-label, long-term (40–52 week) extension study of safety and maintenance of efficacy (includes a 2-week, double-blind, randomised-withdrawal phase at approximately 6 months)
Population	Adults (18–75 years) with EDS associated with narcolepsy	Adults (18–65 years) with EDS associated with narcolepsy	Adults with EDS associated with narcolepsy or OSA who completed:† TONES 2, TONES 3, TONES 4, or Phase 2 studies (TONES 1, ADX-N05 201, 15-004, 15-005)
Intervention (s)	qd, oral (n=177): • Solriamfetol 75 mg • Solriamfetol 150 mg • Solriamfetol 300 mg (unlicensed)	qd, oral (n=44): • Solriamfetol 150 mg/day for weeks 1–4 followed by solriamfetol 300 mg/day (unlicensed) for weeks 5–12	qd, oral (n=643 in open-label phase and n=142 in randomised-withdrawal phase): • Solriamfetol 75 mg • Solriamfetol 150 mg • Solriamfetol 300 mg (unlicensed)
Comparator (s)	• qd, oral placebo (n=59)	• qd, oral placebo (n=49)	• None, except in the 2-week randomised-withdrawal phase conducted in a proportion of patients (planned for up to 300) at approximately 6 months and randomised to placebo (n=142)

Study (Study number)		TONES 2 (Study 14-002)	TONES 1 (Study ADX-N05 202)	TONES 5 (Study 14-005)
Indicate if trial supports application for MA	**Yes**	***X***	***X***	***X***
	No			
Indicate if trial used in the economic model	**Yes**	***X***	***X***	***X***
	No			
Rationale for use/non-use in the model		Provides pivotal comparative efficacy and safety evidence for use in ITC and provides patient level data for use in the model	Provides supporting comparative efficacy and safety evidence for use in ITC	Provides long-term (up to 1 year) data
Reported outcomes specified in the decision problem‡ §		• EDS (**ESS**/MWT) • HRQoL (FOSQ-10, SF-36v2, **EQ-5D-5L**) • Adverse effects of treatment (including AEs, serious AEs, discontinuation)	• EDS (**ESS**/MWT) • Adverse effects of treatment (including AEs, serious AEs, discontinuation)	• EDS (**ESS**) • HRQoL (FOSQ-10, **EQ-5D-5L**, SF-36v2) • Adverse effects of treatment (including AEs, serious AEs, discontinuation)
All other reported outcomes‡		• PGI-c scale • CGI-c scale • WPAI:SHP	• PGI-c scale • CGI-c scale	• PGI-c scale • CGI-c scale • WPAI:SHP

Abbreviations: AE, adverse event; CGI-c; Clinical Global Impression of change; CSR, clinical study report; EDS, excessive daytime sleepiness; EQ-5D-5L, 5-level EQ-5D version ; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire short version; HRQoL, health-related quality of life; ITC, indirect treatment comparison; MA, marketing authorisation; MWT, Maintenance of Wakefulness Test; NICE, National Institute of Health and Care Excellence; OSA, obstructive sleep apnoea; PGI-c, Patient Global Impression of change; qd, once daily; SF-36v2, Short-Form 36-Item Health Survey version 2; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0.
† Patients who completed TONES 2 & TONES 3 formed Group A; patients who completed TONES 4 or the Phase 2 studies TONES 1 (Section B.2.6.2), ADX-N05 201 (Phase 2a, 4-week, double-blind, placebo-controlled, crossover study for EDS in narcolepsy (74)), Study 15-004 or Study 15-005 (ongoing Phase 2 studies in OSA or narcolepsy, respectively) formed Group B.
‡ Outcomes in bold are incorporated in the health economic model.
§ Outcome as defined in NICE scope, with trial outcome/tool in parentheses.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Overview of TONES trials

- The Phase 3 clinical trial programme for solriamfetol in treating EDS in adults with narcolepsy consists of two trials: TONES 2 and TONES 5.
- Additional information from the Phase 2 trial TONES 1 has been included as the results from this trial support the results reported for TONES 2 and TONES 5.

Study design

- TONES 2 (Phase 3, 12-week, double-blind, randomised, placebo-controlled study) was the pivotal RCT for solriamfetol in narcolepsy, and provided data for solriamfetol 75 mg, 150 mg and (unlicensed) 300 mg compared with placebo.
- TONES 1 (Phase 2, 12-week, double-blind, randomised, placebo-controlled study) provides supporting comparative evidence for the solriamfetol 150 mg (first 4 weeks) and (unlicensed) 300 mg daily doses (subsequent 8 weeks), compared with placebo.
- TONES 5 was a Phase 3 long-term, open label-extension study assessing the safety and maintenance of efficacy of solriamfetol for up to 52 weeks, including a 2-week placebo-controlled randomised-withdrawal phase after at least 6 months of treatment to assess the effects of discontinuing solriamfetol. All patients had historically completed another trial in solriamfetol: Group A comprised patients who completed TONES 2 & TONES 3. Group B comprised patients who completed TONES 4 or the Phase 2 studies (TONES 1, ADX-N05 201, 15-004, or 15-005).

Patients enrolled

- TONES 2 enrolled patients with narcolepsy (diagnosed according to the ICSD-3 criteria) who had EDS (Epworth Sleepiness Scale [ESS] score ≥10) and difficulty maintaining wakefulness (mean sleep latency <25 minutes[j], based on the mean of the first four trials of the Maintenance of Wakefulness Test [MWT]).
    - Across solriamfetol groups (including the unlicensed 300 mg dose) [redacted] of patients had prior medication use for narcolepsy and [redacted] had used stimulants; [redacted] had previously used modafinil
- TONES 1 enrolled patients with narcolepsy (diagnosed according to the ICSD-2 criteria[k]) who had EDS (ESS score ≥10[j]) and difficulty maintaining wakefulness (mean sleep latency ≤10 minutes, based on the mean of the first four trials of the MWT).
- In TONES 5, patients were enrolled from previously completed solriamfetol clinical trials, including patients with narcolepsy or OSA (diagnosis was as per the parent study).
    - [redacted] of solriamfetol-treated (including the unlicensed 300 mg dose) patients with narcolepsy reported prior medication use for their narcolepsy; [redacted] had prior stimulant use (including [redacted] who had previously used modafinil).

Overall findings

- As an oral wake-promoting agent, solriamfetol has shown dose-related and clinically and statistically meaningful reductions in EDS in 321 unique patients with narcolepsy across the clinical trial programme (including patients who received the unlicensed 300 mg dose).
- Clinical benefit has been demonstrated versus placebo using validated objective and subjective outcome measures, including the ESS, MWT, Patient Global Impression of Change (PGI-c),

[j] The inclusion criteria for the baseline mean sleep latency was initially ≤10 minutes in TONES 2 but this criterion was increased to <25 minutes as the initial value excluded subjects who were otherwise eligible and were representative of the sleepy narcolepsy population.

[k] TONES 1 used ICSD-2 criteria as the ICSD-3 criteria were not yet published (but were available at the time of TONES 2).

Clinician Global Impression of Change (CGI-c) and 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10).

- Evidence from TONES 2, the supporting Phase 2 RCT TONES 1, and the supporting non-RCT TONES 5 demonstrated the overall safety and tolerability of solriamfetol, and showed that long term treatment has a consistent safety and tolerability profile to that observed with shorter-term clinical trials. The safety profile for solriamfetol is consistent with its pharmacology and is per what would be expected for a dopamine and norepinephrine reuptake inhibitor (DNRI). Solriamfetol within its proposed therapeutic dose range in narcolepsy (75 and 150 mg) is well tolerated by most patients, and in general the adverse effects of solriamfetol are dose-related and appear to be reversible.
- The clinical trial programme demonstrated that the effects of solriamfetol on EDS in narcolepsy are clinically meaningful, rapid in onset (within 1 hour of dosing), and last throughout the day; improvements in ESS scores are maintained long-term (≤52 weeks); mean [SD] exposure in narcolepsy (including the unlicensed 300 mg dose) was [redacted] in TONES 5.

TONES 2 (Pivotal comparative Phase 3 study)

- Solriamfetol 75 and 150 mg reduced sleepiness and/or increased the ability to maintain wakefulness, in patients with narcolepsy and EDS versus placebo, as demonstrated by:
  - A reduction in EDS, shown by a significant decrease in subjective ESS score from baseline to week 12 for solriamfetol 75 and 150 mg doses (least squares [LS] mean difference vs. placebo of -2.2 and -3.8, respectively; both $p<0.05$).
  - An increase in wakefulness, as shown by significant increases in the duration of objective MWT mean sleep latency from baseline to week 12 for solriamfetol 150 mg (LS mean difference vs. placebo 7.7; $p<0.0001$). Numerical improvement was achieved with the 75 mg dose although significance was not reached.
- The magnitude of ESS and MWT effects was dose-dependent, observed as early as week 1 and maintained over the study duration.
- Normal ESS (≤10) scores (see Table 6) were achieved by 30.5% and 40.0% of patients in the solriamfetol 75 mg to 150 mg groups, compared with 15.5% in the placebo group.
- The effects of solriamfetol 150 mg were sustained throughout the day after dosing: at week 12, significant improvements in wakefulness versus placebo were apparent in each of the individual five MWT trials throughout the day (nominal $p<0.05$). Numerical but not significant improvements were observed for the solriamfetol 75 mg dose.
- Solriamfetol led to significantly more patients achieving improvements in their condition, as assessed by the patient and the clinician (using PGI-c and CGI-c, respectively), compared with placebo ($p<0.05$ at all time-points for both doses on PGI-c; $p<0.001$ at all time-points for solriamfetol 150 mg on CGI-c; solriamfetol 75 mg was only significant at week 12 for CGI-c, $p<0.05$). Numerical improvements in FOSQ-10 scores were observed for the solriamfetol 75 and 150 mg doses indicating improved ability to conduct daily activities.
- TONES 2 demonstrated the overall safety and tolerability profile of solriamfetol for treating EDS in narcolepsy; the overall safety and tolerability was consistent with other clinical studies of solriamfetol in narcolepsy.

TONES 1 (Supportive comparative Phase 2 study)

- The results observed in TONES 1 are consistent with those reported for TONES 2.
- At week 4, solriamfetol 150 mg/day significantly reduced sleepiness, and increased the ability to maintain wakefulness, in patients with EDS due to narcolepsy, as demonstrated by significant reductions in ESS and MWT. Solriamfetol also delivered objective and subjective improvements in patient condition, compared with placebo, as assessed using the CGI-c and PGI-c.

TONES 5 (Long-term Phase 3 study)

- Results from the open-label phase of TONES 5 demonstrated that patients with narcolepsy treated with solriamfetol (combined arm, including the unlicensed 300 mg dose) achieved clinically meaningful reductions in mean ESS from baseline[l] that were maintained for up to 40 weeks [redacted] for Group A) or up to 52 weeks [redacted] for Group B).
  - A breakdown of results by dose showed that patients receiving solriamfetol 75 and 150 mg had a reduction in mean ESS that was maintained through to the end of treatment.
- Mean changes in ESS from baseline[l] to week 40 in Group A were [redacted] and [redacted] for the 75 and 150 mg doses, respectively. Mean changes from baseline[l] to week 52 in Group B were [redacted] and [redacted] for the 75 and 150 mg doses, respectively.
- Improvements in QoL, measured using the FOSQ-10, 5-level EQ-5D version (EQ-5D-5L) and 36-item Short Form Health Survey, version 2 (SF-36v2), were maintained during long-term open-label treatment with solriamfetol (combined arm).
- During the randomised withdrawal phase, after 6 months of open label treatment patients with narcolepsy who continued solriamfetol (all doses, including the unlicensed 300 mg dose) maintained their improved EDS status (based on ESS scores), compared with patients who were switched to placebo and who experienced deterioration and worsening EDS status (LS mean difference of [redacted] on ESS; $p<0.0001$); absolute change in ESS was [redacted], [redacted] and [redacted] respectively for patients who were randomised to placebo, 75 mg or 150 mg solriamfetol.
- ESS scores for patients receiving placebo during the randomised withdrawal phase worsened but not beyond baseline scores, indicating that there was no rebound hypersomnia associated with abrupt discontinuation of solriamfetol.
- In TONES 5, solriamfetol discontinuation was not associated with any patterns of withdrawal signs/symptoms or rebound hypersomnia. The safety and tolerability of long-term solriamfetol treatment were consistent with that observed in shorter-term clinical trials.

Conclusions

- TONES 2, TONES 1, and TONES 5 have demonstrated the safety and efficacy of solriamfetol for treating EDS associated with narcolepsy.
- Results were achieved across a range of outcome measures that were clinically meaningful, rapid in onset, lasted throughout the day, and were maintained in the long-term (up to 52 weeks).
- Solriamfetol is well-tolerated and the adverse effects (AEs) observed are consistent with a wake-promoting profile of effects.
- Reversal of treatment benefit upon discontinuation of solriamfetol treatment was observed without any related rebound hypersomnia.

[l] Baseline defined as baseline of the parent study for Group A and baseline of TONES 5 for Group B.

B.2.3.1 Comparative summary of trial methodology

Two Phase 3 trials (TONES 2 and 5) and one supporting Phase 2b trial (TONES 1) provide evidence for solriamfetol for treating EDS in patients with narcolepsy:

- TONES 2 (14-002): 12-week, double-blind, randomised, placebo-controlled study for EDS in narcolepsy
- TONES 1 (ADX-N05 202): 12-week, double-blind, randomised, placebo-controlled study for EDS in narcolepsy
- TONES 5 (14-005): long-term, open-label extension safety and maintenance of efficacy study for EDS in narcolepsy and OSA, including a 2-week placebo-controlled, randomised-withdrawal phase after patients had completed ≥6 months of solriamfetol treatment.

Trial design schematics are provided in Section B.2.3.1.1. The methodologies of these three trials are summarised in Section B.2.3.1.2. Trial endpoints and a description of each endpoint measure are provided in Section B.2.3.1.3.

B.2.3.1.1 Trial design

The solriamfetol 300 mg dose will not be licensed in the UK. However for completeness this dose has been included when describing the study methodology (Section B.2.3.1/B.2.4), baseline characteristics (Section B.2.3.2) and patient flow (Section B.2.4.3).

B.2.3.1.1.1 TONES 2 (Pivotal comparative Phase 3 study)

TONES 2, the pivotal trial for solriamfetol in EDS due to narcolepsy, was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, four-arm parallel-group, 12-week safety and efficacy study, which assessed three doses of solriamfetol compared with placebo in patients with EDS due to narcolepsy. Patients randomised to solriamfetol 150 and (unlicensed) 300 mg doses, received 75 mg and 150 mg doses, respectively on days 1–3 for the first week, and started their full dose from day 4.

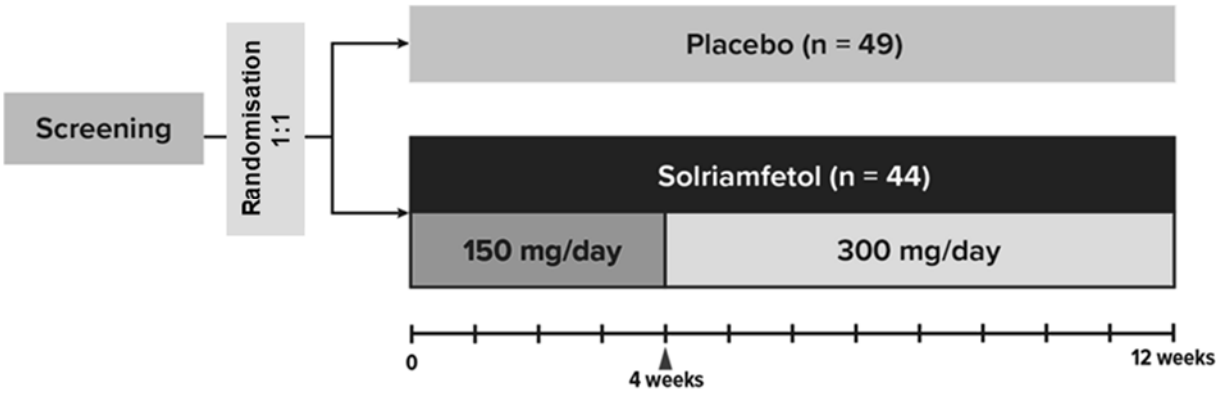
Figure 1. TONES 2 study design (Safety Population)

Abbreviations: TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Adapted from: Thorpy 2019 (77); Dauvilliers 2018 (78).

B.2.3.1.1.2 TONES 1 (Supportive comparative Phase 2 study)

TONES 1 was a Phase 2b, multicentre, randomised, double-blind, placebo-controlled, two-arm parallel-group, 12-week, safety and efficacy study which assessed the efficacy of solriamfetol 150 mg/day for 4 weeks, followed by solriamfetol 300 mg/day (unlicensed) for the subsequent 8 weeks, compared with placebo in patients with EDS due to narcolepsy.

Figure 2. TONES 1 study design (Safety Population)



Abbreviations: TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Adapted from: Ruoff 2016 (75).

B.2.3.1.1.3 TONES 5 (Long-term Phase 3 study)

TONES 5 was a Phase 3, multicentre, open-label, long-term (40–52 weeks) extension study of safety and maintenance of efficacy, which included a 2-week, double-blind, randomised-withdrawal phase at approximately 6 months.

The study enrolled patients with narcolepsy or OSA who had completed prior studies of solriamfetol, and consisted of two groups of patients (due to differences in time elapsed between prior study completion and enrolment in TONES 5):

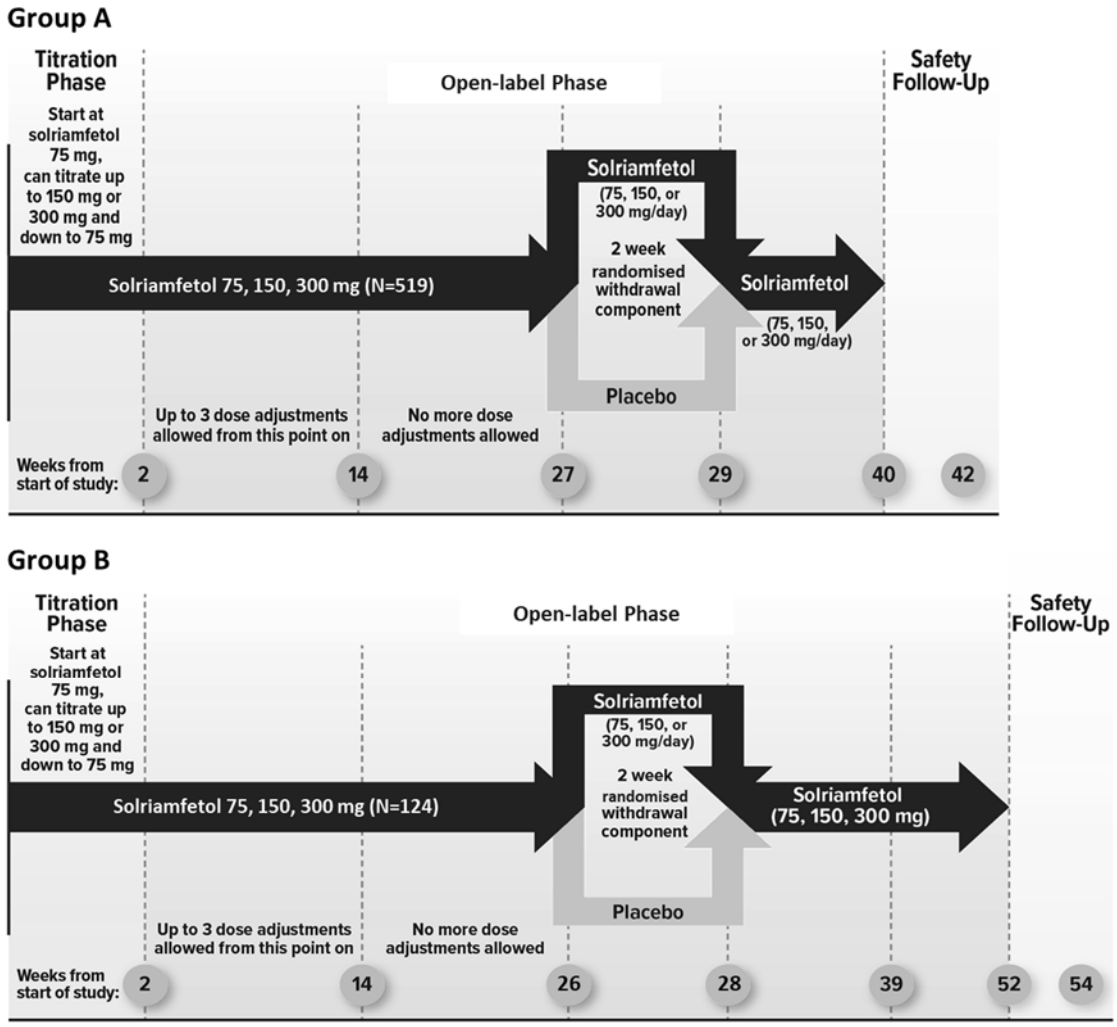
- Group A: patients who enrolled in TONES 5 immediately after completing the 12 week TONES 2 or TONES 3 Phase-3 studies, without a break in treatment between studies; these patients were planned for up to 40 weeks of treatment in TONES 5, to provide up to 52 weeks of continuous efficacy and safety data (total across the parent trial and TONES 5).
- Group B: patients who enrolled in TONES 5 after historically completing the 6-week Phase 3 study TONES 4 or one of the Phase 2 studies (TONES 1 [ADX-N05 202], ADX-N05 201, 15-004, or 15-005); these patients may have

had a break in treatment between completing the parent study and enrolling in TONES 5, thus were planned for up to 52 weeks of treatment in TONES 5.

The study consisted of three phases:

- Titration phase (2 weeks), during which patients initiated open-label solriamfetol 75 mg, and were up-titrated once every 3 days to a maximum tolerated dose (maximum 300 mg, unlicensed).
- Open-label maintenance phase (38 weeks for Group A; 50 weeks for Group B), during which patients continued to receive solriamfetol.
- A double-blind, placebo-controlled randomised withdrawal phase (2 weeks), was conducted (during the open label phase) after approximately 6 months of treatment in a maximum of 300 patients, who were randomised to placebo or to continue their stable dose of solriamfetol for 2 weeks. Following this phase, all placebo-treated patients resumed the same dose of solriamfetol as they were taking prior to withdrawal, for the remainder of the study with a fixed titration, such that patients who were receiving solriamfetol 150 mg per day received solriamfetol 75 mg per day for the first 3 days and were uptitrated back to 150 mg per day thereafter (see Table 4).

Figure 3. TONES 5 study design for Group A and Group B (Safety Population)



Abbreviations: TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Group A comprised patients who completed TONES 2 & TONES 3. Group B comprised patients who completed TONES 4 or the Phase 2 studies (TONES 1, ADX-N05 201, 15-004, or 15-005).
Safety Population for open-label phase: n=643;
Not all patients in the maintenance phase entered the randomised withdrawal phase.
Source: Adapted from Malhotra 2019 (85).

B.2.3.1.2 Description of the trial methodologies for TONES 2, TONES 1 and TONES 5

Table 4 outlines the trial methodology for TONES 2, TONES 1 and TONES 5. An explanation of each of the endpoints and how they are interpreted is provided in Table 5.

Table 4. Comparative summary of trial methodology

Trial no. (acronym)	Study 14-002 (TONES 2)	Study ADX-N05 202 (TONES 1)	Study 14-005 (TONES 5)
Primary study objective	To evaluate the efficacy of solriamfetol administered qd for up to 12 weeks in doses of 75, 150, and 300 mg (unlicensed) compared to placebo in the treatment of excessive sleepiness in adult patients with narcolepsy.	To evaluate the efficacy of solriamfetol administered qd for up to 12 weeks, in a dose range of 150 to 300 mg (unlicensed) per day, compared to placebo in the treatment of EDS in adult patients with narcolepsy.	**Open-label phase:** to evaluate the safety and tolerability of solriamfetol administered qd for up to 52 weeks in doses of 75, 150, and 300 mg (unlicensed). **Randomised withdrawal phase:** to evaluate the maintenance of efficacy of solriamfetol administered qd compared with placebo in adult patients with narcolepsy or OSA after ≥26 weeks.
Secondary study objectives	To evaluate the safety, tolerability and pharmacokinetics of solriamfetol.	To evaluate the safety and tolerability of solriamfetol	**Open-label phase:** to evaluate the open-label maintenance of efficacy of solriamfetol administered qd. **Randomised withdrawal phase:** to evaluate the safety and tolerability of solriamfetol compared with placebo.
Key eligibility criteria	• Adults (18–75 years), narcolepsy diagnosed according to ICSD-3 or DSM-5 criteria. • Baseline ESS score ≥10 • Mean baseline sleep latency <25 minutes on the first four trials of a 40-minute MWT. • Usual nightly sleep time ≥6 hours. • BMI 18 to <45 kg/m^2.	• Adults (18–65 years), narcolepsy diagnosed according to the ICSD-2 criteria • Baseline ESS score ≥10 • Mean baseline sleep latency ≤10 minutes on the first four trials of a 40 minute MWT • Full eligibility criteria are in Appendix L.	Patients met one of the following: • Completed Phase 3 TONES 2 or TONES 3 (Group A) • Completed Phase 3 TONES 4, or Phase 2 (TONES 1, ADX-N05 201, 15-004 or 15-005) (Group B) In addition: • Per the investigator's opinion, the patient was able to take solriamfetol for 40 weeks (Group A), or 52 weeks (Group

Trial no. (acronym)	Study 14-002 (TONES 2)	Study ADX-N05 202 (TONES 1)	Study 14-005 (TONES 5)
	• Full eligibility criteria are in Appendix L.		B), and was able to complete all tests and visits described in the protocol. o Usual night sleep time ≥6 hours • Full eligibility criteria are in Appendix L.
Method of randomisation	• The investigator accessed an IVRS/IWRS to randomise eligible patients. • Randomisation was stratified based on the presence or absence of cataplexy	• A randomisation schedule with appropriate blocking was generated. • A unique identification number (different to the randomisation number) was assigned to each patient who consented. • When the decision was made to randomise a patient, the next available randomisation number from the study drug kits assigned to the site was picked.	Patients participating in 2-week randomised-withdrawal phase only (max. 300 patients): • The investigator accessed an IVRS/IWRS to randomly assign patients to treatment. • Randomisation was stratified by patient diagnosis of narcolepsy or OSA.
Method of blinding (care provider, patient and outcome assessor)	• All study personnel were blinded to the study treatments. • A double-blind approach was used whereby all study drugs were prepared in identical opaque gelatin capsules to ensure adequate blinding.	• All study personnel were blinded to the study treatments. • A double-blind approach was used whereby study drug and placebo were identical in shape and colour, and packaged in matching bottles.	• The titration and maintenance phases of the study were open-label. • A double-blind approach was used during the randomised-withdrawal phase, with patients and all study personnel blinded to treatment. • All study drugs were prepared in identical opaque gelatin capsule to ensure adequate blinding.
Settings/locations where the data were collected	• 59 clinical sites in the US, Canada, Finland, France, Germany, and Italy	• 28 clinical sites in the US	• 79 clinical sites in North America and Europe

Trial no. (acronym)	Study 14-002 (TONES 2)	Study ADX-N05 202 (TONES 1)	Study 14-005 (TONES 5)
Trial drugs	Randomised 1:1:1:1 to receive: • Solriamfetol qd oral 75 mg • Solriamfetol qd oral 150 mg • Solriamfetol qd oral 300 mg (unlicensed) • Matching placebo qd oral Patients randomised to the 150 and 300 mg doses, received 75 mg and 150 mg doses, respectively on days 1–3 for the first week, and started their full dose from day 4. Subjects randomised to the 75 mg dose did not undergo titration. [redacted]	Randomised 1:1 to receive: • qd solriamfetol 150 mg per day during weeks 1–4 and 300 mg (unlicensed) per day during weeks 5–12 • Matching placebo qd • Patients took the drug on an empty stomach within 1 hour of awakening • At the discretion of the investigator, changes in dosing were permitted based on tolerability and efficacy	[redacted] • Titration phase: Patients started on solriamfetol 75 mg qd and were titrated once every 3 or more days to a maximum dose of 300 mg (unlicensed). Down-titration was permitted at any time for safety reasons. Investigators were instructed to titrate patients to the maximal tolerated dose. • Maintenance phase: during which up to 3 dose adjustments were allowed within the first 12 weeks. [redacted] • Randomised withdrawal phase: during which patients were randomised 1:1 to receive placebo or continue their stable dose of solriamfetol. At the end of the withdrawal phase, patients resumed solriamfetol for the remainder of the study, at the dose they were receiving at the beginning of the withdrawal phase.
Permitted and disallowed concomitant medications	• [redacted]	• [redacted] Patients with prior use of medications for the	• Excluded medications varied by patient group (Group A or Group B) and included OTC or prescription medications that could affect evaluation of excessive sleepiness (see Appendix L for details).

Trial no. (acronym)	Study 14-002 (TONES 2)	Study ADX-N05 202 (TONES 1)	Study 14-005 (TONES 5)
	[redacted]	treatment of narcolepsy including any OTC sleep aids or stimulants could enrol provided their last use was at least five half-lives of the drug(s) in question and they had returned to their baseline level of EDS (see Appendix L for details). • [redacted]	• Patients with narcolepsy could have anti-cataplectic medications ([redacted]. • [redacted]
Primary outcomes	See Section B.2.3.1.2		
Other outcomes in the economic model or specified in scope	See Section B.2.3.1.2		
Pre-planned subgroups	• [redacted]	• Presence or absence of cataplexy	• [redacted]

Abbreviations: BMI, body mass index; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; ICSD-3, International Classification of Sleep Disorders-3; IVRS, Interactive Voice Response System; Interactive Web Response System; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; OTC, over the counter; qd, once daily; SNRI, serotonin-norepinephrine reuptake Inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

B.2.3.1.3 Trial outcomes

Trial endpoints for TONES 2, TONES 1, and TONES 5 are outlined in Table 5. An explanation of each of the endpoints and how they are interpreted is provided in Table 6.

Table 5. Endpoints in TONES trials

	TONES 2	TONES 1	TONES 5	
			Open-label phase	**Randomised-withdrawal phase**
Primary efficacy endpoint†	**Co-primary efficacy** • **ESS**: Change from baseline to week 12. • MWT: Change in mean sleep latency time (minutes), from baseline to week 12, determined from first four trials of 40-minute MWT.	**Co-primary efficacy** • MWT: Change in mean sleep latency time (minutes), from baseline to week 12, determined from the first four trials of a 40 minute MWT • CGI-c: Percentage of patients rated as improved at the last assessment.	There was no primary efficacy endpoint during the open-label phase.	**ESS**: Change from the beginning to the end of the randomised-withdrawal period.
Other outcomes used in economic model and/or specified in scope†	**Secondary efficacy** • **ESS**: Change from baseline to weeks 1, 4 and 8. • MWT: Change in mean sleep latency time (minutes), determined from first four trials of a 40-minute MWT 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 five 40 minute MWT trials.	**Secondary efficacy** • **ESS**: Change from baseline to weeks 4 and 12 and over the treatment duration • MWT: Change in mean sleep latency time (minutes), from baseline to week 4, determined from the first four trials of a 40 minute MWT.	*Endpoints were reported separately for Group A and B*. **Efficacy endpoints** • **ESS** (Group A): Change over time from baseline in the parent study, and from last assessment in the parent study. • **ESS** (Group B): Change over time from TONES 5 baseline.	**HRQoL endpoints:** • [redacted] **Safety** • Including AEs, serious AEs, discontinuations

	TONES 2	TONES 1	TONES 5	
			Open-label phase	Randomised-withdrawal phase
	Post-hoc analyses • **ESS**: percentage of patients with a normal ESS score (ESS ≤10; Table 6). **HRQoL** • FOSQ-10 scores. • SF-36v2 scores. • **EQ-5D-5L** dimensions, EQ-VAS and index values. **Safety** • Including AEs, serious AEs, discontinuations.		**HRQoL endpoints:** • FOSQ-10 subscale and total scores. • SF-36v2 domain, mental and physical component, and total scores. • [redacted] **Safety** • Including AEs, serious AEs, discontinuations.	
All other reported outcomes	**Key secondary efficacy** • PGI-c: percentage of patients who reported improvement at week 12. **Secondary efficacy** • PGI-c: percentage of patients who reported improvement at weeks 1, 4 and 8. • CGI-c: percentage of patients reported as improved‡ at weeks 1, 4, 8 and 12. **Productivity** • WPAI:SHP scores.	**Secondary efficacy** • CGI-c: percentage of patients reported as improved‡ at week 4 • PGI-c: percentage of patients who reported improvement **Post-hoc analyses** • MWT: evaluation of the fifth trial of a 40 minute MWT **Exploratory** • Change from baseline in the median number of cataplectic attacks per week	*Endpoints were reported separately for Group A and B.* **Efficacy endpoints:** • PGI-c: percentage of patients who reported improvement‡ from beginning treatment to each time point. • CGI-c: percentage of patients reported as improved‡ from baseline to each time point. **Economic endpoints** • WPAI:SHP.	**Secondary efficacy:** • PGI-c: percentage of patients who reported worsening§ at the end of the randomised withdrawal phase. • CGI-c: percentage of patients reported as worse§ at the end of the randomised withdrawal phase.

	TONES 2	TONES 1	TONES 5	
			Open-label phase	Randomised-withdrawal phase
	Exploratory • Change in the mean and median weekly number of cataplexy attacks in the subgroup of patients with cataplexy • PSG: including total sleep time, number of awakenings, and wake after sleep onset at week 12.	(for the subset of patients with cataplexy)		

Abbreviations: AE, adverse event; CGI-c; Clinical Global Impression of change; EQ-5D-5L, 5-level EQ-5D version ; EQ-VAS, EuroQol visual analogue scale; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire short version; HRQoL, health-related quality of life; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; PGI-c, Patient Global Impression of change; PSG, polysomnography; SF-36v2, Short-Form 36-Item Health Survey version 2; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0.
† **Outcomes in bold** are incorporated in the health economic model.

Table 6. Outcome measures used in the TONES trials

Endpoint	Interpretation
ESS	• The ESS is a validated measure with high specificity and sensitivity for assessing patient-reported subjective sleepiness (87, 88), and provides a measure of a person's general level of daytime sleepiness or their average sleep propensity in daily life (88). • It comprises eight questions, asking the subject how likely they would be to doze off or fall asleep in eight different situations. Responses range from 0=would never doze to 3=high chance of dozing. Total scores range from 0–24 (88), where higher scores represent more severe sleepiness. • Scores ≤10 are considered within the normal range (87-89). • Mean (range) scores in people with EDS due to narcolepsy are 17.5 ± 3.5 (13–23) (88). • A negative change from baseline represents improvement (i.e., a reduction) in sleepiness. The minimum clinically important difference is estimated to be -2 to -3 points (negative score represents improvement) (90-92). • **TONES 2/1/5:** 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.
MWT sleep latency	• The MWT provides a validated objective assessment of the ability to remain awake (wakefulness) (93-95). • Clinical relevance of the MWT is based on the premise that a person's volitional ability to remain awake provides important information regarding their capacity to stay awake and their response to treatment, for a disorder associated with excessive sleepiness (95). • MWT protocols differ by the duration of each wakefulness trial (20 minutes vs. 40 minutes) and MWT results can exhibit a "ceiling effect" in people with normal levels of wakefulness, which is less pronounced with the 40 minute test as the 40 minute test is more challenging and provides a greater distribution of values. Accordingly, the MWT40 may be more appropriate than MWT20 in diagnosing patients with sleep disorders (95). • Measurements of MWT sleep latency using 40-minute trials (MWT40) range from 0 to 40 minutes. Higher latencies indicate greater ability to stay awake, and a positive change from baseline represents improvement (increase) in sleep latency. • Mean sleep latency using MWT40 in normal control patients is reported as 30.4±11.2 minutes by the AASM (95), with 19.4 minutes reported as the lower limit of normal (94). • **TONES 2:** All MWT evaluations were performed subsequent to an overnight stay at the study site for nocturnal PSG according to a standard protocol. • **TONES 1:** All MWT evaluations were performed subsequent to an overnight stay at the study site • **TONES 5:** MWT was not evaluated in this study.
PGI-c	• On the PGI-c, patients rate the change in their condition since they started treatment ranging from 1=very much improved to 7=very much worse. • Improvement was defined as: ratings of "very much", "much", "minimally" improved (96). • Worsening defined as: ratings of "minimally", "much", "very much" worse (97).

Endpoint	Interpretation
CGI-c	• On the CGI-c, investigators rate their impression of any change in the patient's condition from baseline (before the subject started treatment ranging from 1=very much improved to 7=very much worse) (96). • Improvement was defined as: ratings of "very much", "much", "minimally" improved (96). • Worsening defined as: ratings of "minimally", "much", "very much" worse (97).
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 (98). • Functional status is assessed through 5 subscales (activity level, general productivity, social outcome, intimacy and sexual relationships, and vigilance) and a total score (98). • 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 (98). • 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 (99). • 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) (99).
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) (100). • 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") (100).
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 (101, 102). • The validity of the WPAI has been established in a number of diseases (103). • Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (101). A negative change from baseline represents improvement. • **TONES 2:**The WPAI:SHP was used with "narcolepsy" as the SHP. • **TONES 1:** WPAI:SHP was not evaluated in this study. • **TONES 5**: The WPAI:SHP was used with "narcolepsy" or "OSA" as the SHP.

Abbreviations: AASM, American Academy of Sleep Medicine; CGI-c; Clinical Global Impression of change; EDS, excessive daytime sleepiness; EQ-5D-5L, 5-level EQ-5D version ; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire short version; MWT (n), Maintenance of Wakefulness Test (duration in minutes); OSA, obstructive sleep apnoea; PGI-c, Patient Global Impression of change; PSG: polysomnography; QoL, quality of life; SF-36v2, Short-Form 36-Item Health Survey version 2; VAS, visual analogue scale; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0.

B.2.3.2 Baseline characteristics and demographics

B.2.3.2.1 TONES 2 (Pivotal comparative Phase 3 study)

Of the 239 patients who were randomised, 236 received at least 1 dose of study drug (including 75, 150 and 300 mg) and were included in the Safety Population. Based on the Safety Population, baseline demographic and clinical characteristics were similar across treatment groups (Table 7).

- The majority of patients (overall total) were white (80.1%), female (65.3%), with mean body mass index (BMI) of 28.3 kg/m^2.
- The majority of patients (64.4%) were rated by clinicians as being moderately or markedly ill and were characterised by EDS and impaired wakefulness, as indicated by baseline mean (SD) ESS scores of 17.2 (3.2) and MWT sleep latency scores of 7.5 (5.7) minutes, respectively.
- Approximately 39% of patients were rated as markedly ill, as assessed by the Clinician Global Impression of Severity (CGI-s). Using the same tool, approximately 32% of patients were considered to be severely ill or amongst the most extremely ill patients.
- Cataplexy was present in 50.8% of patients, with similar percentages in each treatment group.

Table 7. TONES 2: Baseline demographics and clinical characteristics (Safety Population)

Characteristic†	Placebo N=59	Solriamfetol 75 mg N=59	Solriamfetol 150 mg N=59	Solriamfetol 300 mg (unlicensed) N=59	Solriamfetol Combined N=177
Age, years	36.0 (15.2)	36.5 (12.8)	38.1 (13.0)	34.3 (11.5)	[redacted]
Sex, n (%)					
Male	24 (40.7)	22 (37.3)	17 (28.8)	19 (32.2)	[redacted]
Race, n (%)					
White	47 (79.7)	46 (78.0)	48 (81.4)	48 (81.4)	[redacted]
Black or African American	10 (16.9)	12 (20.3)	6 (10.2)	5 (8.5)	[redacted]
Asian	0	0	3 (5.1)	3 (5.1)	[redacted]
Other	2 (3.4)	1 (1.7)	2 (3.4)	3 (5.1)	[redacted]
BMI, kg/m^2	29.1 (6.0)	27.9 (5.4)	27.9 (5.8)	28.1 (6.3)	[redacted]

Characteristic†	Placebo N=59	Solriamfetol 75 mg N=59	Solriamfetol 150 mg N=59	Solriamfetol 300 mg (unlicensed) N=59	Solriamfetol Combined N=177
Presence of cataplexy, n (%)	29 (49.2)	31 (52.5)	30 (50.8)	30 (50.8)	[redacted]
ESS score§	17.3 (2.8)	17.3 (3.5)	16.9 (3.7)	17.2 (2.8)	[redacted]
MWT sleep latency, minutes‡	6.1 (5.6)	7.5 (5.4)	7.7 (5.6)	8.7 (6.2)	[redacted]
Baseline CGI-s score, n (%)					
1=Normal, not at all ill	0	0	0	0	[redacted]
2=Borderline ill	0	0	0	0	[redacted]
3=Mildly ill	1 (1.7)	3 (5.1)	3 (5.1)	1 (1.7)	[redacted]
4=Moderately ill	14 (23.7)	14 (23.7)	16 (27.1)	17 (28.8)	[redacted]
5=Markedly ill	26 (44.1)	20 (33.9)	24 (40.7)	21 (35.6)	[redacted]
6=Severely ill	13 (22.0)	17 (28.8)	13 (22.0)	12 (20.3)	[redacted]
7=Among the most extremely ill	4 (6.8)	5 (8.5)	3 (5.1)	8 (13.6)	[redacted]
Missing	1 (1.7)	0	0	0	[redacted]

Abbreviations: BMI, body mass index; CGI-s, Clinical Global Impression of Severity; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
† Data are presented as mean (SD) unless otherwise noted.
‡ MWT measures participants' ability to stay awake for a given period of time. Participants were included if their baseline mean sleep latency was <25 minutes on the first four trials of a five-trial, 40-minute MWT.
§ ESS scores range from 0–24, with scores of 16–24 indicating more severe EDS.
Source: Thorpy 2019 (77).

Prior therapy for patients with narcolepsy

- In TONES 2, [redacted] of patients in the placebo arm and [redacted] of patients in the solriamfetol arms (respectively [redacted] and [redacted] of the 75, 150, and 300 mg arms) reported prior use of medications; the classes of medications previously used were consistent with the medical history and symptomatology of patients with narcolepsy:
  - Of the patients in the combined solriamfetol group with prior medication use [redacted] had used stimulants.
  - Almost half of patients had prior use of modafinil ([redacted] placebo; [redacted] combined solriamfetol).
  - A breakdown of the prior use of comparator treatments (as defined in the final NICE scope) by treatment arm in TONES 2 is shown in Table 8.

Table 8. Prior use of comparator treatments by patients in TONES 2 (Safety Population)

Preferred name, n (%)	Placebo N=59	Solriamfetol			
		75 mg N=59	150 mg N=59	300 mg (unlicensed) N=59	All doses N=177
Dexamfetamine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dexamfetamine sulfate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methylphenidate hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methylphenidate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Modafinil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sodium oxybate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: CSR Table 10 (76).

B.2.3.2.2 TONES 1 (Supportive comparative Phase 2 study)

Of the 213 patients who were screened, 93 were enrolled, randomised, received ≥1 dose of study drug (solriamfetol 150/300 mg, n=44; placebo, n=49), and were included in the Safety Population. Based on the Safety Population, the baseline demographic and clinical characteristics were similar across groups (Table 9).

- The majority of patients were white (74.2%), female (64.5%), and mean BMI was 26.6 kg/m^2.
- Baseline mean (SD) ESS score 17.3 (3.3) indicated pathological levels of EDS and baseline mean (SD) MWT sleep latency score was 5.7 (4.5) minutes.
- Cataplexy was present in 35.5% of patients.

Table 9. TONES 1: Baseline demographics and clinical characteristics (Safety Population)

Characteristic†	Solriamfetol N=44	Placebo N=49	Total N=93
Age, years	41.0 (12.3)	36.7 (11.7)	38.7 (12.1)
Sex, n (%)			
Male	14 (31.8)	19 (38.8)	33 (35.5)
Race, n (%)			
White	30 (68.2)	39 (79.6)	69 (74.2)
Black or African American	12 (27.3)	10 (20.4)	22 (23.7)
Other	2 (4.6)	0	2 (2.2)
BMI, kg/m^2	26.8 (4.5)	26.4 (4.4)	26.6 (4.5)

Characteristic†	Solriamfetol N=44	Placebo N=49	Total N=93
Presence of cataplexy, n (%)	17 (38.6)	16 (32.7)	33 (35.5)
MWT sleep latency, minutes‡§	5.7 (5.9)	5.7 (2.8)	5.7 (4.5)
ESS score§ǁ	17.3 (3.7)	17.4 (2.9)	17.3 (3.3)

Abbreviations: BMI, body mass index; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
† Data are presented as mean (SD) unless otherwise noted.
‡ MWT values are the mean of the first four trials of a five-trial, 40-minute MWT.
§ Values of clinical measures at baseline are for the intent-to-treat population (placebo, n=47; solriamfetol, n=43)
ǁ ESS scores range from 0–24, with higher scores indicating more severe EDS.
Source: Ruoff 2016 (75).

B.2.3.2.3 TONES 5 (Long-term Phase 3 study)

This submission pertains to solriamfetol for treating patients with EDS due to narcolepsy, and only baseline characteristics for the narcolepsy population are presented here. Baseline characteristics for the overall population are presented in Appendix L. Baseline characteristics for the patients with OSA are not presented herein but will be provided in the upcoming appraisal of solriamfetol for treating EDS caused by OSA (ID1499).

B.2.3.2.3.1 Open Label Phase

A total of 643 patients (OSA, n=417; narcolepsy, n=226) were included in the overall Safety Population, defined as any patient who took at least one dose of study drug in the open-label phase. Baseline demographic and clinical characteristics of the patients with narcolepsy in TONES 5 are presented in Table 10.

Of the patients with narcolepsy in the overall open-label Safety Population:

- The majority of patients were white (80.1%), female (64.6%), with mean BMI greater than 28 kg/m^2.
- Two-thirds of patients were rated as moderately ([redacted]) or markedly ill (41%), as assessed by the CGI-s. Using the same tool, approximately [redacted] of patients were considered severely ill or among the most extremely ill patients.
- 50.4% of patients with narcolepsy reported having cataplexy at baseline.
- Baseline mean ESS score at the beginning of this study was [redacted] for both Group A and Group B.

Table 10. TONES 5: Baseline demographics and clinical characteristics of patients with narcolepsy† (Safety Population, open-label phase)

Characteristic‡	Combined solriamfetol Narcolepsy N=226
Age, years	38.7 (13.5)
Sex, n (%)	
Male	80 (35.4)
Race, n (%)	
White	181 (80.1)
Black or African American	[redacted]
Other	[redacted]
Presence of cataplexy	114 (50.4)
Body mass index, kg/m^2	28.3 (5.8)
Baseline ESS score‖	17.3 [redacted]
Baseline ESS score§	17.9 ([redacted]
CGI-s, n (%)	
1=Normal, not at all ill	[redacted]
2=Borderline ill	[redacted]
3=Mildly ill	[redacted]
4=Moderately ill	[redacted]
5=Markedly ill	93 (41.2)
6=Severely ill	54 (23.9)
7=Among the most extremely ill	[redacted]
Missing	[redacted]

Abbreviations: CGI-s, Clinical Global Impression of severity; CSR, clinical study report; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness of Test; OSA, obstructive sleep apnoea; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
†TONES 5 included patients with both OSA and narcolepsy. This submission is for solriamfetol for narcolepsy; therefore results for OSA are not presented.
‡ Data are presented as mean (SD) unless otherwise noted.
‖ Baseline ESS score in the parent study (Group A only).
§ Baseline ESS score in the current study (Group B only).
** Baseline CGI-s scores for Group A were obtained from the baseline of the parent study
Source: CSR Table 9, Table 10 (84).

Prior therapy for patients with narcolepsy

- In TONES 5, for the open label phase, [redacted] of patients with narcolepsy reported prior use of medication.
  - The most frequently used prior medications were drugs to treat somnolence or EDS.
  - Of the patients with narcolepsy with prior medication use, 80.1% reported prior stimulant use.
  - [redacted] of patients receiving solriamfetol had prior use of modafinil.
  - A breakdown of the prior use of comparators treatments (as specified in the final NICE scope) by patients in TONES 5 is shown in Table 11.

Table 11. Prior use of comparator treatments by patients in TONES 5 (Safety Population, Open Label Phase)

Preferred name, n (%)	Solriamfetol 75 mg (n=15)	Solriamfetol 150 mg (n=63)	Solriamfetol 300 mg (unlicensed) (n=148)	Combined solriamfetol (n=226)
Dexamfetamine	[redacted]	[redacted]	[redacted]	[redacted]
Dexamfetamine sulfate	[redacted]	[redacted]	[redacted]	[redacted]
Methylphenidate	[redacted]	[redacted]	[redacted]	[redacted]
Methylphenidate hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
Modafinil	[redacted]	[redacted]	[redacted]	[redacted]
Sodium oxybate	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: CSR Table 14.1.8.1a (84).

B.2.3.2.3.2 Randomised withdrawal phase

A total of 282 patients (OSA, n=203; narcolepsy, n=79) were treated in the 2-week randomised withdrawal phase and comprised the Safety Population for that phase.

For subjects in the randomized withdrawal period, baseline disease characteristics were generally similar to those for subjects in the Safety Population of the open-label period.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

The main analysis population sets in the TONES 2, TONES 1, and TONES 5 trials are defined in Table 12. The number of patients in each population set for each trial is provided in Appendix D (Section D.2).

Table 12. Analysis sets used in TONES trials

	TONES 2	TONES 1	TONES 5
Safety Population	• All patients who received ≥1 dose of study drug. • Used for safety evaluations.	• All patients who received ≥1 dose of study drug.	• All patients who received ≥1 dose of study drug. • [redacted]
mITT Population	• All patients who received ≥1 dose of study drug and had a baseline and ≥1 post-baseline evaluation of ESS or MWT. • Used for primary endpoints and other efficacy endpoints.	• All patients who were randomised, received ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment • Used for primary endpoint analyses.	• All patients randomised into the withdrawal phase, received ≥1 dose of study drug in the withdrawal phase, and had evaluable efficacy data at week 29 (Group A) or week 28 (Group B). • Used for analyses of the randomised-withdrawal phase.
Per-Protocol Population	• [redacted]	• [redacted]	• [redacted]

Abbreviations: ESS, Epworth Sleepiness Scale; mITT, modified intent-to-treat; MWT, Maintenance of Wakefulness Test; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

B.2.4.2 Statistical information

A summary of the statistical methods used in the TONES 2, TONES 1 and TONES 5 trials is presented in Table 13.

Table 13. Summary of statistical analyses

Trial number (acronym)	TONES 2	TONES 1	TONES 5
Hypothesis objective	[redacted]	• To evaluate the efficacy of solriamfetol for improvement of wakefulness and reduction of EDS in adults with narcolepsy with or without cataplexy over a lo09nger treatment duration (as compared with Study 201, see Section B.2.2).	**Primary null hypothesis:** [redacted] **Secondary null hypotheses**: • [redacted]
Sample size, power calculation	• Accounting for withdrawals, approximately 240 patients were planned for enrolment, approximately 60 per treatment group. • This sample size was based on an estimate of 54 patients per group to provide at least 80% power to detect a difference of 4 points on the ESS and 6 minutes in mean sleep latency time (from mean of the first 4 trials of the MWT) from baseline to week 12 between each solriamfetol group and placebo. • These estimates were based on the effects observed at the 150 and 300 mg doses in two phase 2 studies (74, 75). This calculation assumed SDs in the changes from baseline of 6 points for ESS and 10	• Sample size calculation was based on the difference in mean change from baseline at week 12 in mean sleep latency for the first four trials of a 40-minute MWT. • A minimum sample size of 41 patients per treatment group was considered sufficient to detect a difference in mean change from baseline in sleep latency times of 3.8 minutes given a pooled SD of 6.0 minutes, a power of 80% and a significance level of 0.05 using a two-sample t-test. • Sample size was increased to 45 patients per group to allow for 10% missing data.	• [redacted] • A sample size of 300 patients in the withdrawal phase, approximately 150 per group, was estimated to provide at least 95% power to detect a difference of 3 points in ESS scores from the beginning to the end of the withdrawal phase. This calculation assumed a common SD of 7 points for the ESS change during the withdrawal phase and a 2-sided significance level of 0.05 using a t-test.

Trial number (acronym)	TONES 2	TONES 1	TONES 5
	minutes for MWT, and a 2-sided significance level of 0.05 using a t test.		
Significance levels and multiplicity	• Fixed hierarchical testing was used to correct for multiplicity, starting with the highest solriamfetol dose for the co-primary endpoints and followed by the key secondary endpoint. • Both co-primary endpoints (ESS and MWT) had to be significant at 0.05 in the primary analysis, for testing to proceed to the key secondary endpoint (PGI-c); testing proceeded to subsequent lower doses with statistical significance claimed only for outcomes above the break in the hierarchy. • Nominal p values are presented for differences below the hierarchical break. • [redacted]	• An α-level was maintained at 0.05 for analyses of both primary endpoints. • No adjustments were made for multiplicity in testing other endpoints.	**In the withdrawal phase:** • To address the multiplicity issue due to multiple efficacy endpoints, a fixed hierarchical testing sequence was employed, starting with ESS and proceeding to PGI-c and CGI-c if the primary endpoint was significant. • Testing stopped when a significance level exceeded 0.05. • For comparisons between solriamfetol and placebo, at the end of the withdrawal phase, patients randomised to solriamfetol were treated as a single group regardless of the dose received. Thus, there were no multiplicity issues with respect to multiple doses in the hypotheses testing.
Statistical analysis	**Co-primary endpoints primary analyses:** • MMRM model, including fixed effects for treatment, visit, treatment by-visit interaction, baseline value of the corresponding endpoint (as a continuous covariate), and randomisation stratification	**Co-primary endpoints primary analyses:** • Comparisons between treatment groups were evaluated using two-sided t-tests **Secondary/Other endpoints:**	**Withdrawal phase** **Primary endpoints primary analyses:** • Evaluated using ANCOVA, [redacted].

Trial number (acronym)	TONES 2	TONES 1	TONES 5
	factor (i.e. presence/absence of cataplexy). • Results are presented as LS mean and SE of treatment difference versus placebo (95% CI). **Co-primary endpoints sensitivity/secondary analyses:** • Four sensitivity analyses were performed to assess the impact of missing data and evaluate the robustness of the primary analysis [redacted] using single imputation approaches (LOCF and mean imputation) and [redacted] using multiple imputation approaches (Markov chain Monte Carlo with regression method and Pattern Mixture model using dropout pattern imputation method). **Secondary/other endpoints:** • PGI-c, CGI-c and EQ-5D-5L Dimensions were analysed using chi-squared tests. • For the other ESS and MWT endpoints and the FOSQ-10, SF-36v2, EQ VAS, EQ-5D-5L Index, and WPAI:SHP endpoints, an MMRM model similar to that used in the primary analysis of the co-primary endpoints was used.	• Percentages of patients (for CGI-c and PGI-c) were evaluated using Fisher's exact test. **Sensitivity Analysis** • ANCOVA was performed as a sensitivity analysis for the primary efficacy endpoint of MWT to confirm treatment differences and evaluated potential site or treatment-by-site interactions. **Post-hoc analysis** • Estimation of the effect size of the mean MWT sleep latency change from baseline was performed post-hoc based on least squares mean divided by SD.	• Results are presented as LS mean treatment difference (95% CI). **Secondary/other endpoints:** • PGI-c and CGI-c were evaluated using a chi-squared test. • [redacted] **Open label phase** • The open-label efficacy endpoints (ESS, PGI-c, and CGI-c) were summarised by [redacted] descriptive statistics [redacted] Where applicable, the changes in ESS from prior study baseline and from the end of the prior study were examined. **Sensitivity/Secondary analyses** • [redacted].
Data management, patient withdrawals	**Primary endpoints** • For primary analysis of the primary endpoints missing data were evaluated using MMRM. Four sensitivity analyses using single and multiple imputation	• Missing data for the co-primary endpoints at week 12 were imputed using LOCF. • Results for assessments of other time points are presented as observed.	**Primary and secondary endpoints** • [redacted] (see "Statistical analysis" in this table).

Trial number (acronym)	TONES 2	TONES 1	TONES 5
	methods were conducted (see "Statistical analysis" in this table). **Other endpoints** • For PGI-c and CGI-c, missing data were imputed using LOCF. • As described under "statistical analysis" in this table, other ESS and MWT endpoints and the FOSQ-10, SF-36v2, EQ VAS, EQ-5D-5L Index, and WPAI:SHP endpoints, were analysed using MMRM. **Post-hoc analyses** • Post hoc analyses assessing patients achieving normal values and clinically meaningful change on the ESS were based on the mITT Population using a LOCF approach.		**Post-hoc analyses** • Post hoc analysis assessing patients achieving normal values on the ESS (ESS ≤10; Table 6) were imputed using a LOCF approach.

Abbreviations: ANCOVA, analysis of covariance; CGI-c; Clinical Global Impression of change; CI, confidence interval; EQ-5D-5L, 5-level EQ-5D version ; EQ-VAS, EuroQol visual analogue scale; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire short version; LOCF, last observation carried forward; LS mean, least squares mean; mITT, modified intent to treat; MMRM, mixed effect repeated measures; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; PGI-c, Patient Global Impression of change; qd, once daily; SD, standard deviation; SE, standard error; SF-36v2, Short-Form 36-Item Health Survey version 2; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0.

† Worsening on PGI-c and CGI-c defined as "minimally", "much", or "very much" worse.

B.2.4.3 Participant flow in the TONES randomised controlled trials

For full details of participant flow for the TONES 2, TONES 1, and TONES 5 trials see Appendix D (Section D.2). Summaries for each trial are provided in the subsequent sections.

B.2.4.3.1 TONES 2

- In total, 364 patients were screened for entry, with 125 screen failures.
- 239 patients were randomly assigned to receive solriamfetol 75 mg ([redacted]), solriamfetol 150 mg [redacted]), solriamfetol 300 mg ([redacted]), or placebo ([redacted]).
- 236 patients were randomised and took at least one dose of study drug (Safety Population);
  [redacted]
- 231 patients successfully completed baseline and at least one post-baseline evaluation of ESS and MWT (modified intent-to-treat [mITT] Population):
  1 patient randomised to placebo and 4 patients randomised to solriamfetol 150 mg did not have a baseline or at least one post-baseline efficacy assessment of ESS and MWT.
- The discontinuation rate was highest in the solriamfetol 300 mg (unlicensed) dose arm (27.1%), with lack of efficacy (n=6, 10.2%) and AEs (n=5, 8.5%) the most common reasons for discontinuation. The next highest discontinuation rate was for solriamfetol 75 mg (16.9%), followed by placebo (10.3%), and solriamfetol 150 mg (7.3%).
  - Discontinuation due to lack of efficacy did not appear to be dose-related.
  - Three of the six patients who discontinued due to lack of efficacy in the 300 mg group and three of the four patients who discontinued due to lack of efficacy in the 75 mg group had cataplexy at screening and had discontinued their anti-cataplectic medication(s) prior to starting study drug on day 1 of the current study.
- Overall, 195 patients completed the study.

B.2.4.3.2 TONES 1

- A total of 213 patients were screened for entry, with 120 screen failures.
- 93 patients were randomly assigned to receive solriamfetol (n=44) or placebo (n=49). All patients received at least one dose of study drug (Safety Population); 3 patients did not have a post-baseline efficacy evaluation; thus 90 patients formed the Intent-To-Treat (ITT) Population.
- The discontinuation rate was highest in the placebo group (22.4%) with patient request (n=5, 10.2%) and lack of efficacy (n=3, 6.1%) the most common reasons for discontinuation.
- 74 patients successfully completed the study and had at least one post-baseline efficacy evaluation (n=38, placebo; n=36 solriamfetol).

B.2.4.3.3 TONES 5

- In total, 651 patients were screened for entry, with 6 screen failures.
  - 645 patients were enrolled in the study and 2 patients withdrew before receiving study drug (1 for other reasons; 1 withdrawal of consent).
  - 643 patients were enrolled and received ≥1 dose of solriamfetol during the open-label phase (Safety Population: n=226 narcolepsy; n=417 OSA).
    - ◊ 519 patients (81%) were from Group A and had completed the TONES 2 or TONES 3 pivotal trials for solriamfetol in narcolepsy or OSA, respectively; these patients were immediately enrolled in TONES 5 without a break in treatment between studies and were planned for up to 40 weeks of treatment in TONES 5 to provide up to 52 weeks of continuous efficacy and safety data in total.
    - ◊ 124 patients (19%) were from Group B and had historically completed TONES 4, or a Phase 2 study (TONES 1, ADX-N05 201, 15-004, or 15-005), before being enrolled in TONES 5. As such these patients may have had a break in treatment between completing the parent study and enrolling in TONES 5 (approximate break in treatment was 2–3 years for patients who completed TONES 1 or Study 201, and ranged from days to weeks for patients who completed TONES 4 or Study 15-004 or 15-005), and thus were planned for up to 52 weeks of treatment in TONES 5.

- A total of 282 patients were randomised into the withdrawal phase (n=142 placebo, n=140 solriamfetol: 13, 46 and 81 patients continued solriamfetol 75 mg, 150 mg and 300 mg, respectively).
  - Of these, 278 completed the withdrawal phase ([redacted] narcolepsy [[redacted] placebo, [redacted] solriamfetol]; [redacted] OSA: [[redacted] placebo, [redacted] solriamfetol]).
- Overall, 458 patients completed the study (n=150 narcolepsy; n=308 OSA).
  - Of the 185 patients who discontinued, the most frequently reported reasons were AEs (9.5%; narcolepsy, 10.2%; OSA, 9.1%), and lack of efficacy (8.4%; narcolepsy, 17.3%; OSA, 3.6%).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A summary quality assessment, in accordance with the NICE recommended checklist for RCT assessment of bias, for the pivotal trial TONES 2 and the supporting trial TONES 1 is provided in Table 14. A complete quality assessment for TONES 2 and TONES 1 is provided in Appendix D. A summary quality assessment for the non-RCT trial TONES 5 is presented below; given that the study was originally set up as a long-term, single arm, non-randomised study, and only a proportion entered the 2-week randomised withdrawal phase, a complete quality assessment using a checklist for non-RCTs is provided in Appendix D.

TONES 2

TONES 2 was a large, randomised, multinational, double-blind, placebo-controlled, well conducted and methodologically robust Phase 3 study. The study protocol and its amendments were approved by an institutional review board or independent ethics committee for each study centre, and the study was conducted in accordance with Good Clinical Practice, and with the Standard Operating Procedures of the contract research organization and Jazz Pharmaceuticals, including the Declaration of Helsinki.

TONES 2 was conducted in a double-blind manner, with patients, investigators and study personnel blinded to study drug treatments. Randomisation to study drug treatment was via a central Interactive Voice or Web Response Service (IVRS/IWRS), and the study drug and placebo were prepared in identical gelatin capsules to ensure adequate blinding. The risk of bias in TONES 2 was low.

TONES 1

TONES 1 was a randomised, double-blind, placebo-controlled, well conducted and methodologically robust Phase 2b study, and is a supporting RCT to TONES 2.

Table 14. Quality assessment results for parallel group RCTs (TONES 2 and TONES 1)

Acronym (Trial number)	TONES 2 (14-002)	TONES 1 (ADX-N05 202)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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
Are conflicts of interest reported?	Yes	Yes
Were concomitant therapies aside from the trial drug(s) allowed?	Yes	Yes
Does treatment administration reflect recommended clinical practice (i.e., initial dose and titration)?	Yes	No

TONES 5

TONES 5 was a large, multinational, open-label, well conducted and methodologically robust Phase 3 extension study that also contained a 2 week, double-blind, placebo-controlled randomised withdrawal component. The study protocol and its amendments were approved by an institutional review board or independent ethics committee for each study centre, and the study was conducted in accordance with Good Clinical Practice, and with the Standard Operating Procedures of the contract research organization and Jazz Pharmaceuticals, including the Declaration of Helsinki.

The randomised withdrawal component of TONES 5 was conducted in a double-blind manner, with patients, investigators and study personnel blinded to study drug treatments. Randomisation to study drug treatment was via a central IVRS/IWRS, and the study drug and placebo were prepared in identical gelatin capsules to ensure adequate blinding.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 TONES 2 (Pivotal comparative Phase 3 study)

Results for the unlicensed 300 mg dose have not been presented

B.2.6.1.1 Treatment exposure in TONES 2

The mean duration of treatment exposure was generally comparable across the placebo and solriamfetol 75 and 150 mg groups, ranging from 74–77 days. The median exposure was 84.0 days for all groups.

B.2.6.1.2 Co-primary efficacy endpoints: ESS and MWT at week 12

The solriamfetol 150 mg dose met the co-primary endpoints of ESS and MWT.

Solriamfetol significantly reduced sleepiness, and increased the ability to maintain wakefulness in patients with EDS caused by narcolepsy, as shown by, respectively:

- Statistically significant improvement in ESS scores compared with placebo for solriamfetol 75 mg (p=0.0211) and 150 mg (p<0.0001) (Table 15, Figure 4).
- Statistically significant improvement in 12-week MWT sleep latency times compared with baseline for the solriamfetol 150 mg dose (p<0.0001). Significance was not achieved for the solriamfetol 75 mg dose (Figure 5).

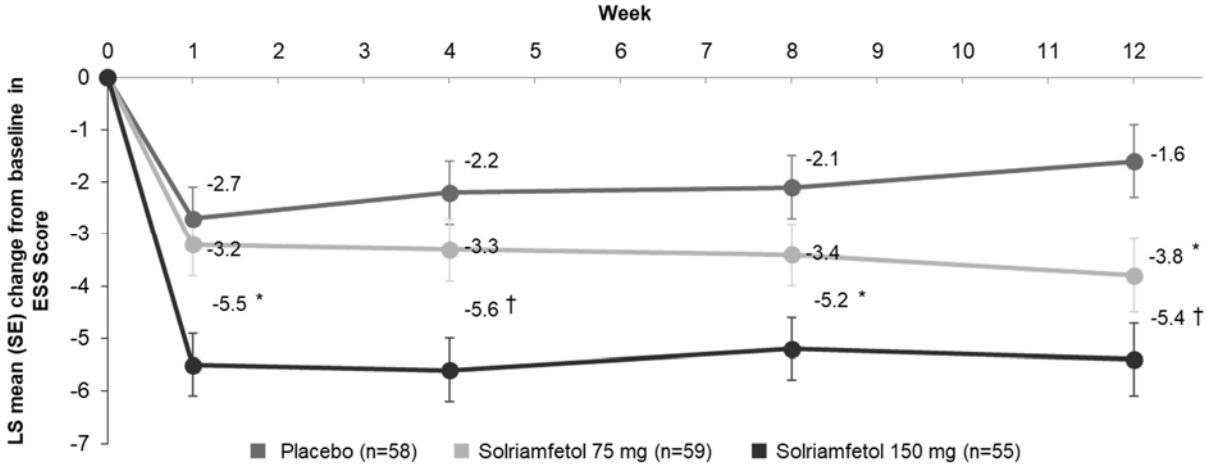
Table 15. TONES 2: Co-primary and key secondary efficacy endpoints (week 12; mITT Population)

	Placebo N=58	Solriamfetol 75 mg N=59	Solriamfetol 150 mg N=55
Co-primary endpoints			
Change in ESS score from baseline to week 12			
LS mean (SE)	-1.6 (0.7)	-3.8 (0.7)	-5.4 (0.7)
LS mean difference vs. placebo		−2.2	−3.8
95% CI		−4.0 to −0.3	−5.6 to −2.0
p value†		0.0211	<0.0001
Change in MWT from baseline to week 12, minutes			
LS mean (SE)	2.1 (1.3)	4.7 (1.3)	9.8 (1.3)
LS mean difference vs. placebo		2.6	7.7
95% CI		−1.0 to 6.3	4.0 to 11.3

	Placebo N=58	Solriamfetol 75 mg N=59	Solriamfetol 150 mg N=55
p value†		0.1595	<0.0001
Key secondary endpoint			
Patients reported improvement (minimally, much, or very much) on PGI-c at week 12			
Yes, n (%)	23 (39.7)	40 (67.8)	43 (78.2)
Difference [yes] from placebo, % (95% CI)		28.1 (10.8 to 45.5)	38.5 (21.9 to 55.2)
p value‡		0.0023§	<0.0001

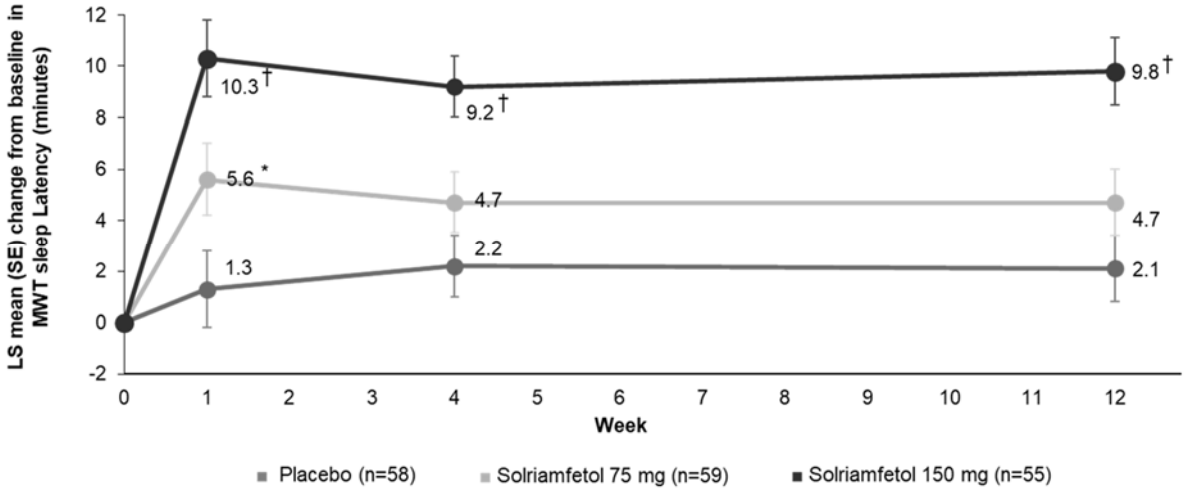
Abbreviations: CI, confidence interval; CSR, clinical study report; ESS, Epworth Sleepiness Scale; LS, least squares; mITT, modified intent to treat; MMRM, mixed effects repeated measures; MWT, Maintenance of Wakefulness Test; PGI-c, Patient Global Impression of change; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
† p-value for MWT and ESS are based on MMRM with change from baseline as response variable and fixed effect of treatment, visit, treatment by visit, randomisation factor, and covariate of baseline value.
‡ p value for PGI-c based on a chi-squared test; percentage of patients reporting improvement on the PGI-c is based on n, the number of patients with non-missing values at week 12.
§ Nominal p value, because it is below the hierarchical break.
Source: Thorpy 2019 (77); CSR Table 13 (76).

Figure 4. TONES 2: Change from baseline on the ESS at weeks 1, 4, 8, and 12 (mITT Population)



Abbreviations: CSR, clinical study report; LS, least squares; ESS, Epworth Sleepiness Scale; mITT, modified intent to treat; MMRM, mixed effects repeated measures; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
* p<0.05, † p<0.0001 vs. placebo. All p values are nominal at weeks 1, 4, and 8.
MMRM with change from baseline as the response variable and fixed effect of treatment, visit, treatment by visit, randomisation stratification factor (presence or absence of cataplexy), covariate of baseline[redacted].
Source: Thorpy 2019 (77); CSR Table 14.2.2.2.1 (76).

Figure 5. TONES 2: Change from baseline in MWT sleep latency at weeks 1, 4, and 12 (mITT Population)



Abbreviations: CSR, clinical study report; LS, least squares; mITT, modified intent to treat; MMRM, mixed effects repeated measures; MWT, Maintenance of Wakefulness Test; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
* p<0.05, † p<0.0001 vs. placebo. All p values are nominal at weeks 1 and 4.
MMRM with change from baseline as the response variable and fixed effect of treatment, visit, treatment by visit, randomisation stratification factor (presence or absence of cataplexy), covariate of baseline, [redacted]
Source: Thorpy 2019 (77); CSR Table 14.2.1.2.1 (76).

B.2.6.1.3 Secondary analysis of co-primary endpoints

[redacted] sensitivity analyses confirmed the robustness of the primary analyses for the co-primary (ESS and MWT) endpoints at solriamfetol 150 mg.

- Four sensitivity analyses of the co-primary endpoints were performed to test the potential impact of missing data and evaluate the robustness of the primary analysis, as described in Section B.2.4.2. All analyses were consistent with and supported the primary analysis.
- [redacted]

B.2.6.1.4 Key secondary endpoint: PGI-c at week 12

- Solriamfetol 75 and 150 mg significantly increased the percentage of patients who reported improvement on the PGI-c compared with placebo at week 12, representing subjective improvements in their condition (Table 15).
- At week 12, increases were dose-dependent and were significant for the solriamfetol 150 mg (78.2%) compared with placebo (39.7%; p<0.0001); the

75 mg dose was nominally significant (67.8%) compared with placebo (p=0.0023), but the comparison was below the hierarchical break.

B.2.6.1.5 Secondary endpoints: ESS

B.2.6.1.5.1 Patients achieving normal and clinically meaningful ESS scores (post-hoc analysis)

- Solriamfetol dose-dependently increased the percentage of patients who reported an ESS score within the normal range (ESS ≤10; see Table 6) after 12 weeks of treatment.
- Of patients receiving solriamfetol 75 and 150 mg, 30.5% and 40.0% respectively, achieved a normal ESS during the trial compared with 15.5% of those patients receiving placebo.

B.2.6.1.5.2 ESS over the study period

- At week 12, solriamfetol 75 and 150 mg significantly reduced ESS scores compared with placebo, indicating reduced EDS (see Section B.2.6.1.1 and Figure 4).
- Effects on the ESS were dose-dependent over the 12 weeks of the study: statistically significant effects were observed at the solriamfetol 150 mg dose as early as week 1 and remained stable over the study duration.

B.2.6.1.6 Secondary endpoints: MWT

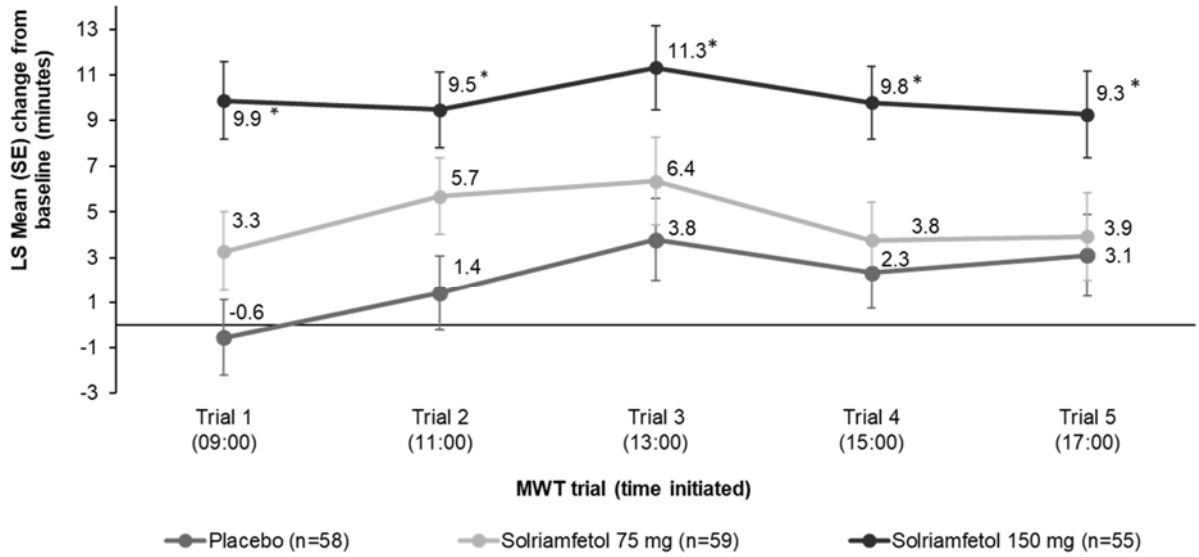
B.2.6.1.6.1 MWT over the study period

- Solriamfetol 150 mg significantly increased MWT mean sleep latency compared with placebo at week 12 (p<0.0001) (see Section B.2.6.1.1 and Figure 5).
- Effects were dose-dependent over the course of the study: statistically significant effects on MWT were observed as early as week 1 at the 150 mg dose (p<0.0001) and remained stable throughout the 12 weeks of the study.

B.2.6.1.6.2 Time course of efficacy on MWT: maintenance of wakefulness throughout the day

- At week 12, the mean change from baseline in each of the five individual MWT trials was greater for solriamfetol 150 mg compared with placebo (indicating improvement in wakefulness) beginning 1 hour after dosing and sustained throughout the day (nominal p<0.05) (Figure 6).

Figure 6. TONES 2: Change from baseline in sleep latency for each of the five individual trials in the MWT at week 12 (mITT Population)



Abbreviations: LS, least squares; mITT, modified intent to treat; MWT, Maintenance of Wakefulness Test; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Note: Individual MWT trials, each of 40-minute duration, were performed at 2-hour intervals at the times shown in parentheses, starting 1 hour after dosing.
* p<0.05 vs. placebo (nominal).
Source: Thorpy 2019 (77).

B.2.6.1.7 Secondary endpoint: PGI-c and CGI-c

- Patient-assessed (PGI-c) and clinician-reported (CGI-c) improvements in the patient's condition were observed with solriamfetol 75 and 150 mg.
- For the PGI-c, statistically significant effects compared with placebo were observed at both doses as early as week 1 and were maintained at weeks 4, 8, and 12:
  - 150 mg: 78.2–89.1%, all p<0.0001; 75 mg: 66.1–71.2%, all p<0.05; placebo: 39.7–53.4%.
- For the CGI-c, both doses of solriamfetol resulted in higher percentages of patients who were reported as improved, with effects for solriamfetol 150 mg significant from week 1 and maintained over the study:
  - 150 mg: 81.8–90.9%, p<0.05 vs placebo at week 1 and p<0.0001 for weeks 4, 8 and 12.
  - 75 mg: 66.1–69.5%, non-significant except p<0.05 vs placebo at week 12.
  - Placebo: 41.4–55.2%.

B.2.6.1.8 HRQoL as measured using FOSQ-10, SF-36v2, EQ-5D-5L

FOSQ-10

- Baseline mean (SD) FOSQ-10 scores were lower than normal values (~18 points; Table 6) across all treatment groups: 12.2 (3.1), 11.4 (3.0), and 11.7 (3.1) in the placebo, solriamfetol 75 , and 150 mg groups, respectively.
- Numerical improvements in function compared with placebo, as assessed by FOSQ-10, were observed for the solriamfetol 75 and 150 mg groups but these did not reach significance (Table 16).

SF-36v2

- Baseline Physical Component Summary (PCS) and Mental Component Summary (MCS) scores on SF-36v2 were low (US Population Mean T-Score=50) (104) and similar to previously reported values in adults with narcolepsy (PCS score: ~44; MCS score: ~41) (105).
  - Baseline mean (SD) SF-36v2 PCS scores were 47.5 (8.8), 47.4 (8.0), and 44.4 (7.3) in the placebo, solriamfetol 75 and 150 mg groups, respectively.
  - Baseline mean (SD) SF-36v2 MCS scores were 47.6 (8.3), 42.9 (10.6), and 46.2 (8.7) in the placebo, solriamfetol 75 and 150 mg groups, respectively.
- At week 12, there were no statistically significant changes in PCS or MCS summary scores for solriamfetol compared with placebo (Table 16), however at week 12 both doses of solriamfetol significantly improved the Vitality domain, and solriamfetol 75 mg significantly improved General Health (all $p<0.05$).

EQ-5D-5L

- For the EQ-5D-5L dimensions of mobility, self-care, performance of usual activities, pain and discomfort, and anxiety/depression, no meaningful trends were observed for any solriamfetol dose compared with placebo during the study.
- Across the dimensions of the EQ-5D-5L, the LS mean change from baseline for solriamfetol 75 and 150 mg ranged from [redacted], and [redacted] respectively, compared with [redacted] for placebo.
- No meaningful trends were observed for mean changes from baseline in EuroQol Visual Analogue Scale (EQ-VAS) scores or in EQ-5D-5L index scores for any solriamfetol dose compared with placebo during the study (Table 16).

- At baseline, [redacted] of patients in TONES 2 had utility scores=1, and therefore reported no disutility due to their narcolepsy. The lack of meaningful trends in EQ-5D scores in the narcolepsy population is of uncertain cause. Given the substantial negative impact that narcolepsy has on QoL (see Section B.1.3), 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. Further discussion on the suitability of EQ-5D in the narcolepsy population and relevance to economic modelling is discussed in Section B.3.4.

Table 16. 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]
Change in EQ-5D-5L Index from baseline to week 12†			
LS mean (SE)	0.03 (0014)	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

	Placebo N=58	Solriamfetol 75 mg N=59	Solriamfetol 150 mg N=55
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

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.
Source: Thorpy 2017 (106); Thorpy 2018 (82); CSR Table 26, Table 14.2.6.2, Table 14.2.7.2, Table 14.2.9.2 and Table 14.2.10.1 (76).
† 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.

B.2.6.1.9 Work productivity and activity impairment: specific health problem (WPAI:SHP) scale

At baseline, the majority of patients in TONES 2 who were employed reported work and activity impairment. After 12 weeks of treatment, solriamfetol 150 mg decreased the rates of presenteeism (impairment while working), decreased overall work impairment, and reduced activity impairment outside of work (all nominal $p<0.05$).

B.2.6.1.10 Conclusion

In conclusion, solriamfetol demonstrated dose-dependent efficacy that was significantly superior to placebo on the co-primary endpoints of ESS and MWT at 12 weeks for the solriamfetol 150 mg dose. The 75 mg dose resulted in significantly greater improvement than placebo on the ESS but not on the MWT (although the study was not powered for the 75mg dose). Improvements on both co-primary endpoints were observed at week 1 for solriamfetol 150 mg, and maintained over the study duration, indicating that patients did not build a tolerance to solriamfetol treatment over 12 weeks. Furthermore, on the MWT significant effects were observed compared with placebo across each of the five individual MWT trials for solriamfetol 150 mg; at 12-weeks, these effects were observed 1 hour after dosing, and lasted throughout the day.

Overall, this Phase 3 study demonstrated the robust effects of solriamfetol for improving EDS in a large population of patients with narcolepsy, with associated improvements in functioning and HRQoL.

B.2.6.2 TONES 1 (Supportive comparative Phase 2 study)

B.2.6.2.1 Treatment exposure in TONES 1

At week 4, all patients who were randomised to receive solriamfetol were taking the 150 mg/day dose and all patients were up-titrated to the solriamfetol 300 mg dose (unlicensed) from week 5 for the remainder of the study; five patients had their dose reduced to 150 mg/day between week 5 and the week 12 visit. Of the patients randomised to solriamfetol who completed the study, 31 (86.1%) were taking the 300 mg/day dose (unlicensed) at the final visit.

B.2.6.2.2 Efficacy endpoints assessed at week 4 in TONES 1

TONES 1 investigated the effects of solriamfetol 150 mg for 4 weeks followed by 300 mg for a subsequent 8 weeks. The co-primary endpoints of change in MWT and CGI-c at week 12 were met, however as the 300 mg dose is unlicensed these results are not presented. All endpoints are reported for week 4, at which time point all patients were receiving solriamfetol 150 mg.

At week 4, solriamfetol 150 mg significantly reduced EDS (ESS), improved the ability to maintain wakefulness (MWT), increased the proportion of patients rated as improved by clinicians (CGI-c), and increased the proportion of patients self-reported as improved (PGI-c) compared with placebo.

B.2.6.2.2.1 ESS at week 4

- Solriamfetol significantly reduced mean ESS scores from baseline [redacted] compared with placebo (mean reduction [redacted], respectively; [redacted]).
- A significant difference in mean ESS scores was observed between the solriamfetol and placebo arms from week 1 post-treatment ($p<0.0001$) and maintained through week 4.

B.2.6.2.2.2 MWT at week 4

- The mean change from baseline in sleep latency was significantly greater with solriamfetol 150 mg compared with placebo for each of the MWT trials at week 4 ($p<0.05$).
- Changes from baseline at week 4 ranged from 11.7 (period 1) to 5.4 minutes (period 5) with solriamfetol 150 mg compared with 1.6 (period 1) to -4.0 minutes (period 5) for placebo.
- At week 4 the mean (standard error [SE]) change from baseline in average sleep latency for the first four trials of a five-trial MWT was 9.5 (1.3) for solriamfetol 150 mg compared with 1.4 (1.1) for placebo ($p<0.0001$).

B.2.6.2.2.3 CGI-c at week 4

A significantly higher proportion of patients receiving solriamfetol were reported as improved on the CCI-c at weeks 1 and 4 compared with placebo:

- Improvements were observed from week 1, with 83.7% of patients receiving solriamfetol 150 mg reporting improvement compared with 55.3% of patients receiving placebo ($p=0.0058$).
- These effects were maintained through week 4, with 80.0% of patients receiving solriamfetol 150 mg reporting improvement at week 4, compared with 51.1% of patients receiving placebo ($p=0.0066$).

B.2.6.2.2.4 PGI-c at week 4

A significantly higher proportion of patients receiving solriamfetol were improved on the PGI-c at weeks 1 and 4 compared with placebo:

- Effects were observed from week 1, with 83.7% of patients receiving solriamfetol 150 mg reporting improvement compared with 53.2% of patients receiving placebo ($p=0.0030$).
- The effects on PGI-c were maintained through week 4, with 82.5% of patients receiving solriamfetol 150 mg reporting improvement at week 4, compared with 44.4% of patients receiving placebo ($p=0.0003$).

B.2.6.2.3 Conclusion

The results from this Phase 2 study (TONES 1) support those observed in TONES 2, the pivotal Phase 3 trial for solriamfetol in narcolepsy. Patients who received

solriamfetol 150 mg/day for 4 weeks achieved significant reductions in EDS (as assessed using ESS), and significant improvements in their ability to stay awake (as assessed using MWT). A greater proportion of patients receiving solriamfetol were rated by clinicians and patients as improved (using the CGI-c and PGI-c, respectively) compared with placebo.

B.2.6.3 TONES 5 (Long-term Phase 3 study)

As described previously (Section B.2.4.3.3), patients in TONES 5 had either narcolepsy or OSA (Safety Population: n=226 narcolepsy; n=417 OSA), and were classified as Group A or Group B depending on which original trial (hereafter 'parent trial') the patients were enrolled into TONES 5 from:

- Group A (n=519; 81%) included patients from TONES 2 and TONES 3; the baseline values used for analysis were the baseline values of the parent study.
- Group B (n=124; 19%) included patients from TONES 4, or one of the phase 2 studies: 15-004, 15-005, or ADX-N05-201, or TONES 1; the baseline values used for analysis were the baseline values of TONES 5.

This submission pertains to solriamfetol for treating patients with EDS due to narcolepsy, and only results for the narcolepsy population are presented. Results for the overall population are presented in Appendix L. Results for patients with OSA are not presented here but will be provided in the upcoming appraisal of solriamfetol for treating EDS due to OSA (ID1499). Results are generally only presented as the pre-specified single, combined dose arm (75, 150 and 300 mg), with the exception of ESS change over time, where a separate analysis by dose has also been presented.

B.2.6.3.1 Treatment exposure in TONES 5

Across the entire duration of the study, patients with narcolepsy who received solriamfetol (all doses, including the unlicensed 300 mg dose) had a mean (SD) treatment exposure of [redacted]; [redacted] days for 75 mg, [redacted] for 150 mg and [redacted] for 300 mg, reflecting the ability to titrate up from the 75 mg dose. When analysed by modal dose (dose level most frequently received during the study) mean (SD) treatment exposure was [redacted] for 75 mg,

[redacted] for 150 mg and [redacted] for 300 mg. The dose split by modal dose was: 75 mg, [redacted] 150 mg, [redacted]; 300 mg, [redacted]

B.2.6.3.2 Open-label phase

B.2.6.3.2.1 Secondary efficacy endpoint: ESS

- During the open-label phase, the long-term maintenance of solriamfetol efficacy was demonstrated in the narcolepsy population through sustained reduction in mean ESS scores, indicating reduced EDS.
- These effects were maintained for up 40 weeks in Group A (Figure 7), and up to 52 weeks in Group B (Figure 8).
- Patients with narcolepsy who were treated with solriamfetol (combined group) achieved clinically meaningful reductions in mean ESS (defined as ≥3 point decrease) after 2 weeks of treatment, that were maintained for up to 40 weeks for Group A and up to 52 weeks for Group B:
  - Group A[m] mean change from baseline to week 2, [redacted], and week 40, [redacted].
  - Group B[m] mean change from baseline to week 2, [redacted], and week 52, [redacted].

Results by dose group

- Results for the change in ESS from baseline to week 2, and to week 40 and 52 for the solriamfetol 75 and 150 mg doses, respectively, is provided in Table 17, showing that the beneficial treatment effect of solriamfetol was maintained over the long term with the 75 and 150 mg doses.

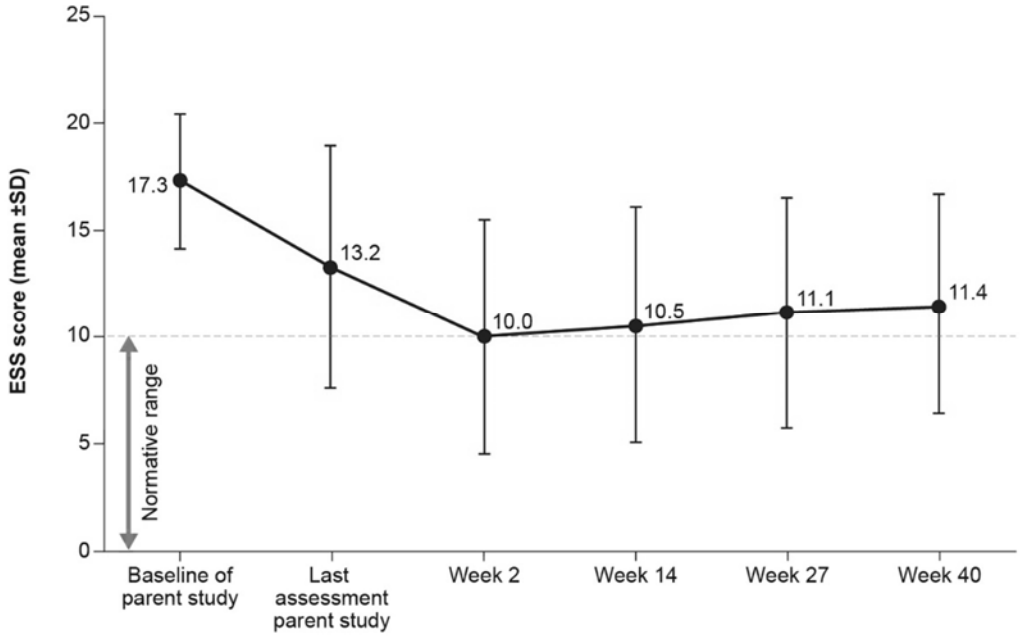
[m] Group A (n=519; 81%) included patients from TONES 2 and TONES 3; the baseline values used for analysis were the baseline values of the parent study. Group B (n=124; 19%) included patients from TONES 4, or one of the phase 2 studies: 15 004, 15-005, or ADX-N05-201, or TONES 1; the baseline values used for analysis were the baseline values of TONES 5.

Table 17. 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	150 mg	75 mg	150 mg
Change from baseline† at week 2	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline† at week 40	[redacted]	[redacted]	NA	NA
Change from baseline† at week 52	NA	NA	[redacted]	[redacted]

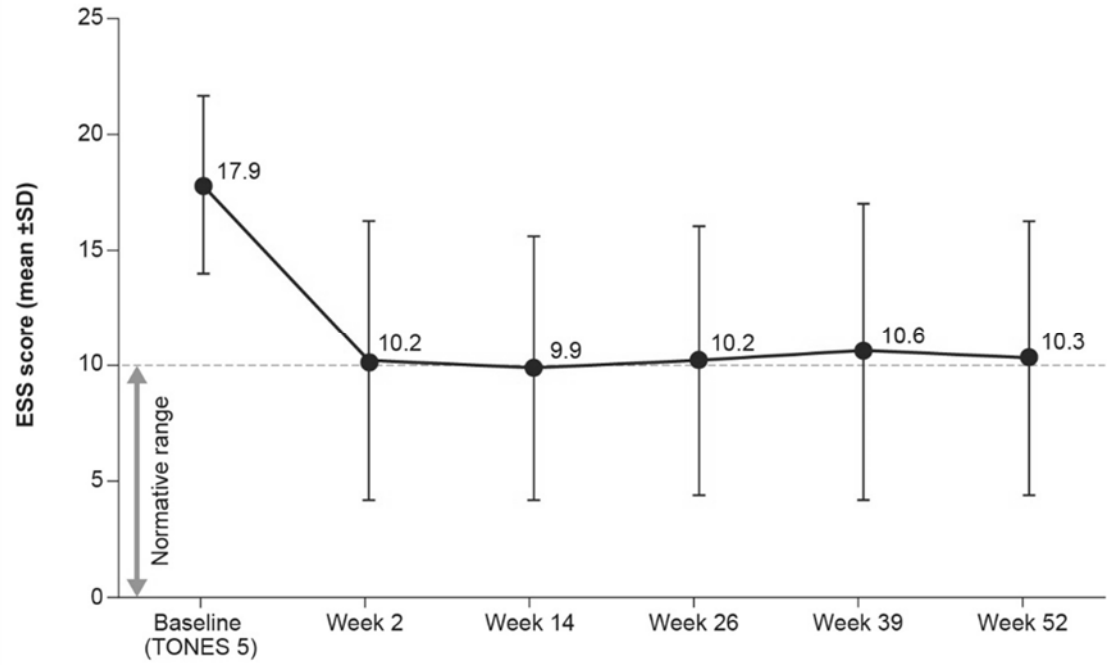
Abbreviations: NA, not applicable; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Data presented as mean (SD).
† Baseline defined as the baseline of the parent study for Group A and baseline of TONES 5 for Group B.

Figure 7. TONES 5: mean (SD) ESS score for patients with narcolepsy in Group A (n=186) during the open-label phase (Safety Population)



Abbreviations: ESS, Epworth sleepiness scale; OSA, obstructive sleep apnoea; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: Malhotra 2019 (85).

Figure 8. TONES 5: mean (SD) ESS score for patients with narcolepsy in Group B (n=40) during the open-label phase (Safety Population)



Abbreviations: ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: Malhotra 2019 (85).

B.2.6.3.2.2 Secondary endpoints: PGI-c and CGI-c

- Long term maintenance of solriamfetol efficacy was demonstrated by sustained improvements in PGI-c and CGI-c scores.
- The majority of patients with narcolepsy had improvements in the PGI-c and CGI-c at week 2 (≥94.1% and ≥94.6%, respectively), with similar percentages maintained at each assessment; at the final assessment, 86.8–87.1% reported improvement in PGI-c, and 88.2–89.5% were reported improved on the CGI-c.

B.2.6.3.2.3 HRQoL as measured using FOSQ-10, SF-36v2, EQ-5D-5L

FOSQ-10

- During the open-label phase, mean FOSQ-10 scores increased from baseline in the narcolepsy population for patients in Group A and Group B.
- Increased FOSQ-10 scores were observed by week 14, and were maintained for the duration of solriamfetol treatment in Group A and B, indicating less difficulty performing everyday activities (Figure 9 and Figure 10, respectively).

Figure 9. Mean (SD) FOSQ-10 scores for patients with narcolepsy in Group A (n=185) during the open-label phase (Safety Population)

Abbreviations: FOSQ, Functional Outcomes of Sleep Questionnaire; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: Weaver 2019 (86); CSR Table 14.2.4.1a (84).

Figure 10. Mean (SD) FOSQ-10 scores for patients with narcolepsy in Group B (n=40) during the open-label phase (Safety Population)

Abbreviations: FOSQ, functional outcomes of sleep questionnaire; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: CSR Table 14.2.4.1a (84).

SF-36v2

- Solriamfetol (combined arm including the unlicensed 300 mg dose) improved both PCS and MCS scores and these improvements were maintained for the duration of treatment.
- The vitality domain had the largest magnitude of change however there was high variability between the patients on all domain scores suggesting the SF-36v2 has limited sensitivity to detect change in this population.
  - Patients with narcolepsy in Group A achieved numerical improvements from baseline to week 40 in the PCS (+2.8) and MSC (+4.5), in addition to a 10.3 point improvement in the vitality domain. Similar results were observed for patients with narcolepsy in Group B.

EQ-5D-5L

- [redacted] when measured at various time points up to the final evaluation (Group A, week 40; Group B, week 52).
- [redacted] for both Group A and Group B (mean changes ranged from [redacted] respectively).

B.2.6.3.2.4 Economic endpoint: WPAI:SHP

- Long-term treatment with solriamfetol (combined arm, including the unlicensed 300 mg dose) led to decreased rates of presenteeism (impairment while working), overall work impairment and activity impairment outside of work, in patients with narcolepsy.
- For patients with narcolepsy in Group A and Group B:
  - Presenteeism, overall work impairment and impairment of activities outside of work were reduced by at least 25% from baseline.
  - These improvements were observed by week 14 of treatment and were maintained throughout the duration of the study (up to 52 weeks).

– The percentage of work time missed was [redacted], respectively) and small decreases from baseline were observed with solriamfetol treatment [redacted] respectively).

B.2.6.3.3 Randomised withdrawal phase

B.2.6.3.3.1 Primary efficacy endpoint: ESS

- All primary and secondary endpoints were met for the subgroup of patients with narcolepsy in the 2-week randomised withdrawal phase.
- During this phase, patients with narcolepsy who continued solriamfetol (all doses including unlicensed 300 mg) maintained their treatment benefit (LS mean change in ESS[redacted]) compared with patients randomised to placebo (LS mean change in ESS: [redacted]), resulting in a significant LS mean difference of [redacted](95% confidence interval [CI],[redacted]).
- There was no rebound hypersomnia observed in patients randomised to placebo, as demonstrated by ESS scores after withdrawal that did not exceed baseline ESS scores (Figure 11).
- The primary and secondary endpoints were met in the overall population; full results are reported in Appendix L.

Figure 11. ESS scores for participants with narcolepsy (Group A and Group B) who entered the randomised withdrawal phase (mITT Population)

[redacted]

Abbreviations: CI, confidence interval; ESS, Epworth Sleepiness scale; LS, least squares.
† Values are for the baseline of parent study for Group A (n=66) and at baseline of current study for Group B

(n=12); the randomised withdrawal phase included participants from both groups.
Source: CSR Table 20 and Table 14.2.1.2a (84).

Table 18. Primary analysis: change in ESS from efficacy baseline to end of randomised withdrawal phase† (mITT Population)

	Placebo N=40	Solriamfetol combined N=38
LS mean (SE)	[redacted]	[redacted]
LS mean difference		[redacted]
95% CI		[redacted]
p value‡		[redacted]

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CSR, clinical study report; ESS, Epworth Sleepiness scale; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; OSA, obstructive sleep apnoea; SE, standard error.
†End of randomised withdrawal phase: week 29 for Group A; week 28 for Group B.
‡p values for ESS based on ANCOVA
[redacted] Analysis conducted in the mITT population[redacted].
Source: CSR Table 20 (84).

Secondary analysis of the primary endpoint

B.2.6.3.3.2 [redacted]**Secondary endpoints: PGI-c and CGI-c**

- During the 2 week withdrawal phase, patients receiving placebo had a loss of efficacy whereas those receiving solriamfetol (combined arm including the unlicensed 300 mg dose) maintained efficacy.
  - [redacted] of patients in the placebo group reported worsening on the PGI-c compared with [redacted] of patients in the solriamfetol group ([redacted]).
- From the beginning to the end of the withdrawal phase, clinicians reported a statistically significantly [redacted] of patients receiving placebo had experienced worsening, compared with patients receiving solriamfetol [redacted] vs. [redacted], respectively[redacted]).
- Full PGI-c and CGI-c results are provided in Appendix L.

B.2.6.3.3.3 HRQoL endpoint (FOSQ-10)

- At the end of the randomised withdrawal phase, mean FOSQ-10 scores were [redacted] for patients with narcolepsy who received placebo, compared with patients who received solriamfetol ([redacted] respectively).
- The LS mean difference was [redacted] in the narcolepsy population ([redacted]).

B.2.6.3.4 TONES 5 conclusion

Long-term efficacy for EDS, as measured by ESS, was maintained in patients with narcolepsy when receiving up to 52 weeks of open-label treatment with solriamfetol (combined arm, including unlicensed 300 mg dose). When analysed by licensed dose groups (75 and 150 mg) effects were also maintained over time. After at least 6 months of open-label treatment, patients with narcolepsy who received solriamfetol during a 2-week randomised-withdrawal phase maintained their treatment-related improvements, whereas those who received placebo worsened (LS mean difference of [redacted] TONES 5 results demonstrated the long-term maintenance of efficacy with continued solriamfetol treatment, and a loss of solriamfetol benefit upon withdrawal of treatment, without any related rebound hypersomnia.

B.2.7 Subgroup analysis

B.2.7.1 TONES 2 (Pivotal comparative Phase 3 study)

Pre-specified subgroup analyses were based on the mITT Population and were performed using the Mixed-Model Repeated Measures (MMRM) method used for the primary endpoint analysis (see Section B.2.4.2).
[redacted]. A summary of results is provided below, with full results provided in Appendix E.

- **The presence or absence of cataplexy:** Demographic characteristics were generally similar between participants with and without cataplexy. Subgroup analyses did not suggest any clinically meaningful differences in efficacy at 12 weeks between patients with narcolepsy with/without cataplexy. From baseline to week 12, solriamfetol 150 mg significantly decreased ESS scores and significantly increased sleep latency on MWT in both subgroups.

- [redacted]

B.2.7.2 TONES 1 (Supportive comparative Phase 2 study)

Analyses of the primary and secondary endpoints within the subgroup of patients with cataplexy was an exploratory endpoint in TONES 1. A total of [redacted] patients out of the [redacted] patients in the ITT Population had cataplexy. This subgroup of patients had [redacted] to the overall ITT population with regards reduction in EDS and improvement in ability to maintain wakefulness.

B.2.7.3 TONES 5 (Long-term Phase 3 study)

For the 2-week randomised-withdrawal phase, pre-specified subgroup analyses to evaluate ESS were performed on the mITT Population, [redacted] (see Section B.2.4.2). Pre-defined subgroups were [redacted] Narcolepsy and OSA were also specified and relevant data have already been presented in the main results for TONES 5 in Section B.2.3.2.3.

Demographics and clinical characteristics for subgroups were not defined. A summary of results is provided below, with full results in Appendix E.

- For the 2-week randomised-withdrawal phase [redacted] did not appear to affect the findings from the overall population, i.e. that switching to placebo leads to a significant deterioration in ESS score compared with solriamfetol (combined arm including unlicensed 300 mg dose).
- [redacted] When the same analyses were performed using the Per Protocol Population, results were consistent with those observed in the mITT Population.

B.2.8 Meta-analysis

Not applicable.

B.2.9 Indirect and mixed treatment comparisons

Overview of ITC

- In the absence of direct evidence for solriamfetol and comparators of interest, an ITC was conducted to elicit estimates of relative effectiveness. The clinical SLR (see Section B.2.1) sought evidence for inclusion in the ITC for dexamfetamine, methylphenidate, sodium oxybate and pitolisant, in line with the company decision problem and anticipated positioning of solriamfetol in UK clinical practice.
- The clinical SLR (described in Section B.2.9.1) shows there is a general paucity of evidence available supporting treatments used in narcolepsy and which could subsequently be utilised in the ITC; no ITC-appropriate evidence was identified for dexamfetamine or methylphenidate, while pitolisant analyses had to be restricted to combined dose analyses, in the absence of effectiveness estimates stratified by dose.
- The ESS, a subjective measure of EDS, and the MWT an objective measure of wakefulness, are two key clinical outcomes common to the RCTs identified in the clinical SLR, and assessed in the ITC.
- In the base-case analysis of ESS, solriamfetol 150 mg was associated with a similar beneficial impact (CrI for relative effectiveness crossed zero) on EDS versus pitolisant (≤40 mg; estimates stratified by pitolisant dose are not available from pitolisant trials). Compared with sodium oxybate, solriamfetol 150 mg demonstrated improvements (CrIs for relative effectiveness did not cross zero) over the 3 and 4.5 g doses, numerical improvements (CrIs crossed zero) over the 6 g dose, and numerical deficits relative to the highest 9 g dose (CrIs crossed zero).
- A potential beneficial effect of concomitant therapies (e.g. methylphenidate, modafinil) leading to overestimation of comparator efficacy could not be ruled out; scenario analyses excluding sodium oxybate trials that allowed concomitant therapies were inconclusive. All pitolisant trials allowed concomitant therapies

and as such a scenario analysis to test the impact of concomitant therapies was not possible.

- Outcomes from the ESS analysis were subsequently utilised in the economic model described in Section B.3.2.
- Efficacy analyses on the objective MWT supported the positive findings on the ESS analysis, but also demonstrated improvement on this objective outcome for solriamfetol 150 mg versus pitolisant (CrIs did not cross zero). Despite results from ESS analysis being broadly similar, the MWT effect was more apparent and highlights additional evidence for the improved efficacy of solriamfetol compared with pitolisant.
- The efficacy analyses across the ESS and MWT in the ITC suggest that solriamfetol is at least as effective, and in some cases more effective, than pitolisant and sodium oxybate.
- Analyses of safety outcomes showed that incidence of AEs was similar across all treatments analysed with the exception of the 150 mg dose of solriamfetol; however, there were no significant differences (CrIs for relative effectiveness crossed zero) in the incidence of discontinuations resulting from AEs nor for overall rates of serious AEs.
- There was no evidence of a suitable quality identified to allow methylphenidate or dexamfetamine to be incorporated into the ITC – no RCTs were identified, while four observational studies did not include control arms that allowed incorporation into the evidence networks; the paucity of evidence is supported by EFNS Guidelines on the Management of Narcolepsy in Adults from 2011 (13).

B.2.9.1 Methodology

In the absence of direct evidence from trials, an ITC was conducted to compare efficacy and safety outcomes of solriamfetol versus relevant comparators, to inform the de novo cost-effectiveness analysis.

Table 19 provides a summary of the RCTs used to inform the ITC, showing that solriamfetol could be compared with pitolisant and sodium oxybate (via the common comparator of placebo). There was no evidence of a suitable quality identified to

allow methylphenidate or dexamfetamine to be incorporated into the ITC (either from RCTs or from observational studies). This paucity of evidence is supported by EFNS Guidelines on the Management of Narcolepsy in Adults (2011) (11). In line with the company decision problem described in Section B.1.1 which reflects the anticipated positioning of solriamfetol in patients who have failed, have a contraindication to or are intolerant to modafinil, modafinil was not considered as a comparator for the ITC.

Table 20 provides an overview of endpoints available for each treatment, with associated time points of measurement.

Results are presented in Section B.2.9.2 for outcomes used to directly inform data inputs in the economic model, namely ESS scores. Supporting endpoints (MWT and overall safety endpoints [AEs, serious AEs and discontinuation due to AEs]) are summarised and then presented in full in Appendix D. Other outcomes collected during the SLR and assessed during the ITC, but which were not considered further in the economic model have not been presented.

Summary details of the clinical SLR to identify solriamfetol and comparator studies to inform an ITC are provided in Section B.2.1 with full details of the SLR and ITC methodology provided in Appendix D.

Table 19: Summary of the RCTs used to carry out the indirect treatment comparison

References of trial†	Solriamfetol 75 mg qd	Solriamfetol 150 mg qd	Pitolisant ≤40 mg qd	Sodium Oxybate 3 g qd	Sodium Oxybate 4.5 g qd	Sodium Oxybate 6 g qd	Sodium Oxybate 9 g qd	Placebo
TONES 2 (76)	✓	✓						✓
TONES 1 (75)		✓						✓
Dauvillier, 2013 (107)			✓					✓
Szakacs, 2017 (108)			✓					✓
Xyrem, 2002 (109) (110)				✓		✓	✓	✓
Xyrem, 2005 (111-114)					✓	✓	✓	✓
Black, 2006 (115)						✓	✓	✓

Abbreviations: qd, once daily; RCT, randomised controlled trial; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
† Study name is based on the primary citation as listed in Appendix D (Table 6).

Table 20. Endpoints of interest assessed in the ITC

Outcome	Timepoint, week	Solriamfetol 75 mg qd	Solriamfetol 150 mg qd	Pitolisant ≤40 mg qd	Sodium Oxybate 3 g qd	Sodium Oxybate 4.5 g qd	Sodium Oxybate 6 g qd	Sodium Oxybate 9 g qd	Placebo
Efficacy outcomes									
ESS	4	✓	✓	✓	✓	✓	✓	✓	✓
	8	✓	✓	✓		✓	✓	✓	✓
MWT20	8	✓	✓					✓	✓
MWT40	4	✓	✓			✓	✓	✓	✓
	8	✓	✓	✓		✓	✓	✓	✓
SF-36 PCS	8	✓	✓			✓	✓	✓	✓
SF-36 MCS	8	✓	✓			✓	✓	✓	✓
CGI-C	8	✓	✓	✓		✓	✓	✓	✓
PGI-C	8	✓	✓	✓					✓
Safety outcomes									
Any AE	NA	✓	✓	✓				✓	✓
Serious AE	NA	✓	✓	✓		✓	✓	✓	✓
AE leading to discontinuation	NA	✓	✓	✓		✓	✓	✓	✓

Abbreviations: AEs, adverse events; CGI-c, clinician global impression of change; ESS, Epworth Sleepiness Scale; MCS, mental component summary; MWT20, 20 minute Maintenance of Wakefulness Test; MWT40, 40 minute Maintenance of Wakefulness Test; NA, not applicable; PCS, physical component summary; PGI-c, patient global impression of change; qd, once daily; SF-36, Short-form 36-item health survey; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

B.2.9.2 Results

General information relating to results presentation is presented below. Results of the ITC for each endpoint are presented in the subsequent sub-sections (B.2.9.2.1 to B.2.9.2.5).

Network diagrams: All network diagrams for each outcome at each timepoint were constructed using all available data, as per Table 19 and Table 20. Each node (circle) represents a treatment arm from an included study, and each edge (straight line) represents a direct comparison made within a given trial. The number centred on each edge indicates the number of trials contributing a direct comparison.

Relative effects, absolute effects, and uncertainty:

- The relative effect (i.e., the effect of drug vs placebo) of solriamfetol 150 mg (reference treatment for analysis) versus the relative effect of comparators at each timepoint was expressed for all comparators as a mean difference from baseline to endpoint for ESS, MWT, and as a risk difference for all safety outcomes.
- The absolute outcome values for all treatments were calculated by combining the ITC-derived treatment effect estimate with the placebo effect (calculated as a weighted average across all placebo arms).
- Uncertainty around point estimates for relative and absolute change from baseline was measured by the 95% credible interval (CrI). Determinations of significance were made based on whether the 95% CrI crossed the line of no effect (1 for odds ratio and 0 for mean difference).

Fixed and random effects: Relative and absolute effects are presented using fixed and random effects models. A fixed effects model assumes that the true treatment effect is identical across studies, with sampling error as the only contributor to the estimate. A random effects model estimates study-specific treatment effects.(116) Fixed-effect would be the preferred choice for most of the results given very similar or slightly lower deviance information criterion (DIC), lack of significant heterogeneity, and small evidence base consisting of few trials, wherein nearly all networks had only one trial per pairwise comparison.

Rank probabilities fixed effects: The Bayesian framework used in the ITC enables the generation of rank probabilities for each intervention at each timepoint. These probabilities convey an estimate that a particular intervention will be best among comparators for showing the greatest change in a given outcome. The rank probabilities of solriamfetol and all comparators using the fixed effect model are expressed as a decimal between 0-1, with higher numbers indicating the likelihood of the treatment achieving the rank as listed on the column heading.

Model fit statistics: The model fit statistics listed below were used to compare models (117):

- The posterior mean of the deviance (Dbar) is a measure of the goodness of fit for a model representing the posterior mean of the deviance. A lower Dbar value represents a model which would best predict a dataset with the same structure as the observed values.
- The effective number of parameters (pD) is the difference between the posterior mean of deviance and deviance at posterior means of the parameters of interest. pD is a measure of model complexity which is penalized for having more effective parameters.
- The DIC is the sum of Dbar and pD, where the smallest DIC value represents a good model fit.

B.2.9.2.1 ESS week 4

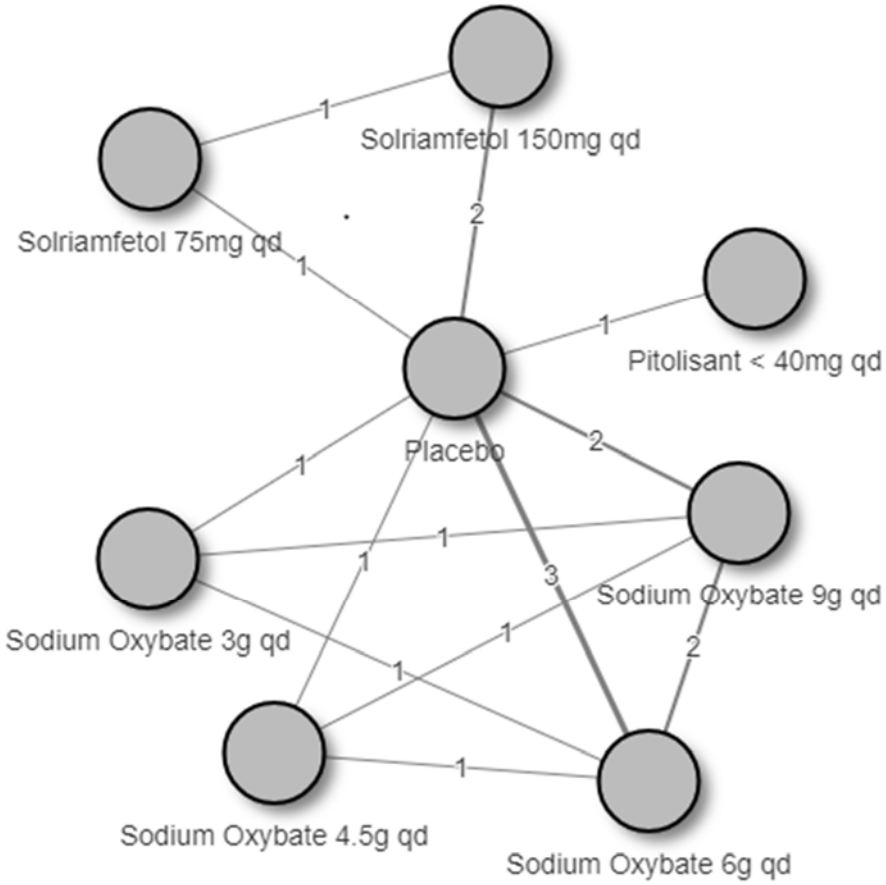
The network of evidence for the ESS outcome at week 4 is presented in Figure 12. Fixed effects analyses on absolute treatment effects show all treatments improved ESS from baseline, although lower doses of sodium oxybate (3 and 4.5 g) showed no improvement versus placebo (Table 21).

Analysis of relative treatment effects (fixed effects) showed the following:

- Solriamfetol vs pitolisant:
  - Solriamfetol 150 mg showed numerical improvement (CrI for relative effectiveness crossed zero) on ESS versus pitolisant (≤40 mg; estimates stratified by pitolisant dose are not available from pitolisant trials).
- Solriamfetol vs sodium oxybate:
  - Solriamfetol 150 mg showed improvement on ESS over sodium oxybate 3 and 4.5 g (CrI for relative effectiveness did not cross zero), numerical improvement over the 6 g dose (CrIs crossed zero) and a small numerical deficit to the highest 9 g dose (CrIs crossed zero).

Random effects analyses produced similar results, in terms of the size of the relative effects estimated.

Figure 12.ESS week 4 network diagram



Abbreviations: ESS, Epworth Sleepiness Scale; qd, once daily.

Table 21. ESS week 4 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	-3.305	-3.306	0.664	(-4.604, -2.005)	-3.28	-3.283	1.078	(-5.406, -1.166)
Solriamfetol 75 mg	-2.255	-2.257	0.805	(-3.83, -0.674)	-2.24	-2.239	1.371	(-4.976, 0.477)
Pitolisant ≤40 mg	-0.507	-0.508	1.253	(-2.962, 1.947)	-0.48	-0.474	1.915	(-4.256, 3.304)
Sodium Oxybate 3 mg	-3.763	-3.763	1.053	(-5.832, -1.706)	-3.72	-3.712	1.711	(-7.124, -0.338)
Sodium Oxybate 4.5 g	-3.835	-3.835	1.055	(-5.901, -1.757)	-3.81	-3.807	1.714	(-7.216, -0.415)
Sodium Oxybate 6 g	-1.447	-1.448	0.846	(-3.101, 0.218)	-1.42	-1.427	1.377	(-4.158, 1.3)
Sodium Oxybate 9 g	0.744	0.744	0.905	(-1.031, 2.522)	0.78	0.791	1.473	(-2.124, 3.694)
Absolute Treatment Effects								
Placebo	-1.565	-1.57	0.26	(-2.066, -1.064)	-1.55	-1.551	0.257	(-2.054, -1.046)
Solriamfetol 75 mg	-2.616	-2.62	0.76	(-4.098, -1.135)	-2.59	-2.601	1.344	(-5.257, 0.108)
Solriamfetol 150 mg	-4.871	-4.87	0.6	(-6.044, -3.702)	-4.83	-4.837	1.036	(-6.876, -2.77)
Pitolisant ≤40 mg	-4.364	-4.36	1.06	(-6.453, -2.284)	-4.36	-4.362	1.585	(-7.455, -1.221)
Sodium Oxybate 3 g	-1.108	-1.11	0.79	(-2.644, 0.43)	-1.12	-1.126	1.309	(-3.681, 1.49)
Sodium Oxybate 4.5 g	-1.036	-1.03	0.77	(-2.558, 0.48)	-1.03	-1.033	1.306	(-3.607, 1.583)
Sodium Oxybate 6 g	-3.423	-3.42	0.46	(-4.318, -2.527)	-3.41	-3.411	0.821	(-5.041, -1.769)
Sodium Oxybate 9 g	-5.615	-5.61	0.56	(-6.715, -4.511)	-5.61	-5.618	0.976	(-7.555, -3.665)

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.

Table 22. ESS week 4 model fit statistics

	Model Fit Statistics	
	Fixed effects	Random effects
pD	13	14.83
Dbar	33.581	33.102
DIC	46.58	47.932
Total Residual Deviance	16.7	16.21

Abbreviations: Dbar, posterior mean of the deviance; DIC, deviance information criterion; ESS, Epworth Sleepiness Scale; pD, effective number of parameters.

Table 23. ESS week 4 rank probabilities fixed effects

Rank	1	2	3	4	5	6	7	8
Placebo	0.000	0.000	0.000	0.000	0.054	0.527	0.338	0.081
Solriamfetol 75 mg	0.000	0.002	0.049	0.190	0.580	0.108	0.047	0.023
Solriamfetol 150 mg	0.173	0.502	0.293	0.031	0.001	0.000	0.000	0.000
Sodium Oxybate 3 g	0.000	0.000	0.000	0.004	0.069	0.188	0.316	0.423
Sodium Oxybate 4.5 g	0	0	0	0.004	0.059	0.168	0.297	0.472
Sodium Oxybate 6 g	0	0.018	0.197	0.608	0.175	0.002	0	0
Sodium Oxybate 9 g	0.697	0.244	0.058	0.001	0	0	0	0
Pitolisant ≤40 mg	0.129	0.234	0.402	0.162	0.062	0.007	0.002	0.001

Abbreviations: ESS, Epworth Sleepiness Scale.

Table 24. ESS week 4 rank probabilities random effects

Rank	1	2	3	4	5	6	7	8
Placebo	0.000	0.000	0.001	0.009	0.095	0.454	0.344	0.097
Solriamfetol 75 mg	0.010	0.024	0.082	0.200	0.400	0.134	0.086	0.064
Solriamfetol 150 mg	0.202	0.415	0.282	0.073	0.018	0.006	0.003	0.001
Sodium Oxybate 3 g	0.001	0.005	0.011	0.028	0.102	0.184	0.281	0.388
Sodium Oxybate 4.5 g	0.001	0.004	0.01	0.026	0.091	0.168	0.263	0.437
Sodium Oxybate 6 g	0.005	0.05	0.218	0.486	0.207	0.026	0.007	0.001
Sodium Oxybate 9 g	0.61	0.273	0.092	0.018	0.005	0.001	0	0
Pitolisant ≤40 mg	0.171	0.228	0.304	0.161	0.082	0.027	0.016	0.011

Abbreviations: ESS, Epworth Sleepiness Scale.

B.2.9.2.2 ESS week 8

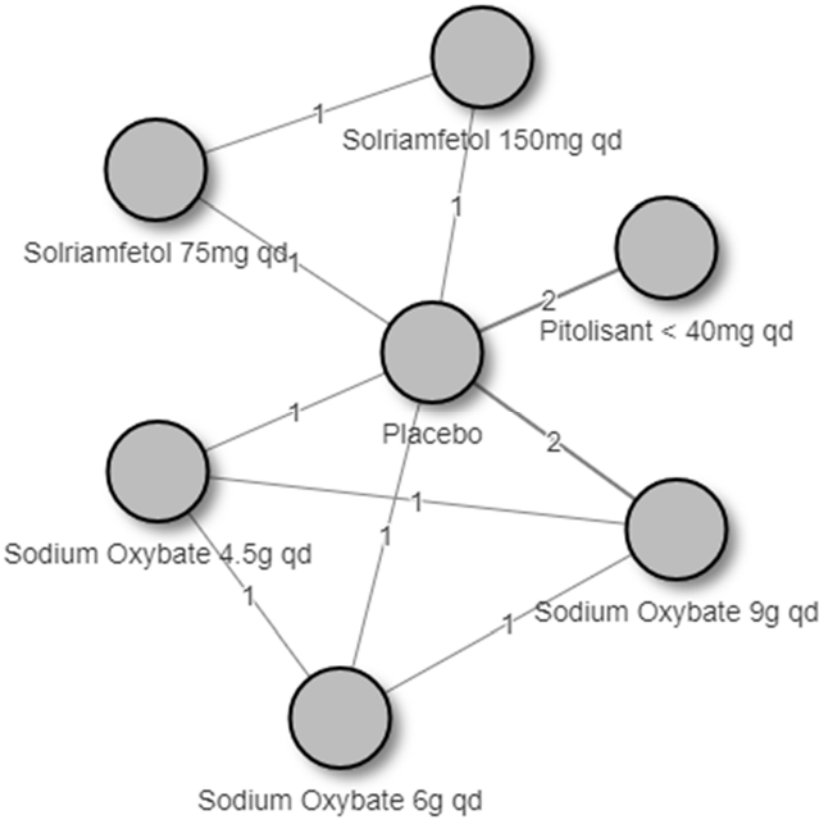
The network of evidence for the ESS outcome at week 8 is presented in Figure 13. Fixed effects analyses on absolute treatment effects show all treatments improved ESS from baseline, although the lowest dose of sodium oxybate with data available (4.5 g) showed no improvement versus placebo (Table 25).

Analysis of relative treatment effects (fixed effects) showed the following:

- Solriamfetol vs pitolisant:
  - Solriamfetol 150 mg showed similar improvement (CrI for relative effectiveness crossed zero) on ESS versus pitolisant (≤40 mg; estimates stratified by pitolisant dose are not available from pitolisant trials).
- Solriamfetol vs sodium oxybate:
  - Solriamfetol 150 mg showed improvement on ESS over sodium oxybate 4.5 g (CrI for relative effectiveness did not cross zero), a numerical improvement over the 6 g dose (CrIs crossed zero), and a small numerical but not significant deficit to the highest 9 g dose (CrIs crossed zero).

Random effects analyses produced similar results, in terms of the size of the relative effects estimated.

Figure 13. ESS week 8 Network Diagram



Abbreviations: ESS, Epworth Sleepiness Scale; qd, once daily.

Table 25 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)

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.

Table 26 ESS week 8 model fit statistics

	Model Fit Statistics	
	Fixed effects	Random effects
pD	11.002	12.103
Dbar	28.099	28.094
DIC	39.102	40.196
Total Residual Deviance	12.48	12.48

Abbreviations: Dbar, posterior mean of the deviance; DIC, deviance information criterion; ESS, Epworth Sleepiness Scale; pD, effective number of parameters.

Table 27 ESS week 8 rank probabilities fixed effects

Rank	1	2	3	4	5	6	7
Placebo	0.000	0.000	0.000	0.005	0.100	0.397	0.498
Solriamfetol 75 mg	0.001	0.008	0.060	0.458	0.300	0.132	0.042
Solriamfetol 150 mg	0.209	0.330	0.392	0.059	0.009	0.001	0.000
Sodium Oxybate 4.5 g	0.000	0.001	0.008	0.061	0.190	0.333	0.407
Sodium Oxybate 6 g	0.001	0.018	0.075	0.331	0.386	0.136	0.053
Sodium Oxybate 9 g	0.564	0.298	0.128	0.01	0	0	0
Pitolisant ≤40 mg	0.225	0.345	0.336	0.076	0.016	0.002	0

Abbreviations: ESS, Epworth Sleepiness Scale.

Table 28 ESS week 8 rank probabilities random effects

Rank	1	2	3	4	5	6	7
Placebo	0.000	0.002	0.014	0.057	0.196	0.371	0.361
Solriamfetol 75 mg	0.034	0.069	0.119	0.297	0.215	0.145	0.122
Solriamfetol 150 mg	0.251	0.264	0.274	0.106	0.054	0.032	0.020
Sodium Oxybate 4.5 g	0.011	0.026	0.052	0.106	0.181	0.253	0.370
Sodium Oxybate 6 g	0.029	0.064	0.121	0.238	0.274	0.163	0.111
Sodium Oxybate 9 g	0.448	0.29	0.164	0.067	0.021	0.008	0.002
Pitolisant ≤40 mg	0.227	0.285	0.257	0.13	0.06	0.028	0.014

Abbreviations: ESS, Epworth Sleepiness Scale.

B.2.9.2.3 MWT outcomes

The network of evidence for the MWT40 outcome at week 8 is presented in Appendix D, Figure 6. Fixed effects analyses on absolute treatment effects show all treatments improved MWT from baseline, although sodium oxybate 6 g showed only small improvement versus placebo (Appendix D, Table 35).

Analysis of relative treatment effects (fixed effects) showed the following:

- Solriamfetol vs pitolisant:
  - Solriamfetol 150 mg showed a (CrI for relative effectiveness did not cross zero) improvement on MWT versus pitolisant (≤40 mg; estimates stratified by pitolisant dose are not available from pitolisant trials).

- The relative impact of pitolisant was similar to that of the lowest solriamfetol dose (75 mg).
- Considering ESS and MWT collectively for this comparison supports an overall conclusion that solriamfetol may be at least as effective, if not superior to pitolisant in managing the symptoms of EDS in narcolepsy.

- Solriamfetol vs sodium oxybate:
  - Solriamfetol 150 mg showed improvement (CrI for relative effectiveness did not cross zero) on MWT over sodium oxybate 4.5 g and sodium oxybate 6 g, and a numerical deficit to the highest 9 g dose (CrIs crossed zero).

Random effects analyses produced similar results, in terms of the size of the relative effects estimated, as did analyses of MWT20 at week 8 (Appendix D, Table 27) and MWT40 at week 4 (Appendix D, Table 31).

B.2.9.2.4 Safety outcomes

The networks of evidence for the safety outcomes are presented in Appendix D, Figure 7 to Figure 9. Analyses of safety outcomes showed that all treatments were associated with AEs, with the incidence of AEs being similar across all treatments analysed with the exception of the higher dose of solriamfetol (150 mg); however the rates of discontinuations due to AEs and of serious AEs were low and there were no significant differences between treatments (CrI for relative effectiveness crossed zero).

B.2.9.2.5 Scenario analyses

Use of primary endpoint timepoint for solriamfetol (12 weeks)

While base case analyses endeavoured to compare like with like in terms of timepoints analysed (i.e. 4 weeks and 8 weeks), it should be acknowledged that the primary endpoint of the solriamfetol TONES 2 trial was 12 weeks. A scenario was conducted to compare 12-week outcomes for solriamfetol at 75 or 150 mg against the last available timepoint (7 weeks or later) for comparator trials. In this analysis the following trials were excluded:

- TONES 1 (Ruoff, 2016 (75)): The solriamfetol dose at 12 weeks was 300 mg and will not be licensed.

- Xyrem, 2002 (109): The trial was only 4 weeks long and hence the timepoint was considered too short to include.

Table 29. RCTs included in the scenario analysis

	Solriamfetol 75 mg qd	Solriamfetol 150 mg qd	Pitolisant ≤40 mg qd	Sodium Oxybate 3 g qd	Sodium Oxybate 4.5 g qd	Sodium Oxybate 6 g qd	Sodium Oxybate 9 g qd	Placebo
TONES 2 (76)	✓	✓						✓
Dauvillier, 2013 (107)			✓					✓
Szakacs, 2017 (108)			✓					✓
Xyrem, 2005 (111-114)					✓	✓	✓	✓
Black, 2006 (115)						✓	✓	✓

Abbreviations: qd, once daily; RCT, randomised controlled trial; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
† Study name is based on the primary citation as listed in Appendix D (Table 6).

Table 30. Endpoints of interest assessed in the scenario analysis

	ESS	MWT20	MWT40
TONES 2 (76)	✓	✓	✓
Dauvillier, 2013 (107)	✓		✓
Szakacs, 2017 (108)	✓		✓
Xyrem, 2005 (111-114)	✓		✓
Black, 2006 (115)	✓	✓	

Abbreviations: ESS, Epworth Sleepiness Scale; MWT20, 20 minute Maintenance of Wakefulness Test; MWT40, 40 minute Maintenance of Wakefulness Test; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

Results for ESS at week 12 are presented below. Additional information (model fit statistics, rank probabilities), along with full results for MWT 20 and MWT 40 at 12 weeks are presented in Appendix D, Section D.1.5.6)

Table 31. ESS week 12 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	-3.797	-3.799	0.925	(-5.612, -1.986)	-3.8	-3.796	2.176	(-8.462, 0.789)
Solriamfetol 75 mg	-1.596	-1.595	0.939	(-3.437, 0.242)	-1.593	-1.583	2.179	(-6.24, 3.022)
Pitolisant ≤40 mg	-0.656	-0.659	1.253	(-3.107, 1.788)	-0.741	-0.711	2.728	(-6.585, 4.931)
Sodium Oxybate 4.5 g	-3.646	-3.648	1.343	(-6.276, -1.017)	-3.673	-3.679	3.003	(-10.04, 2.66)
Sodium Oxybate 6 g	-2.647	-2.648	1.339	(-5.276, -0.023)	-2.671	-2.671	3.008	(-9.05, 3.674)
Sodium Oxybate 9 g	-0.044	-0.047	1.176	(-2.347, 2.262)	-0.047	-0.048	2.677	(-5.724, 5.63)
Absolute Treatment Effects								
Placebo	-1.249	-1.248	0.324	(-1.884, -0.613)	-1.243	-1.243	0.325	(-1.878, -0.61)
Solriamfetol 75 mg	-3.449	-3.453	0.887	(-5.18, -1.711)	-3.449	-3.452	2.151	(-8.043, 1.128)
Solriamfetol 150 mg	-5.046	-5.046	0.88	(-6.775, -3.322)	-5.043	-5.044	2.157	(-9.657, -0.467)
Pitolisant ≤40 mg	-4.39	-4.389	0.793	(-5.945, -2.84)	-4.302	-4.327	1.623	(-7.635, -0.834)
Sodium Oxybate 4.5 g	-1.4	-1.4	0.903	(-3.171, 0.364)	-1.37	-1.368	2.04	(-5.702, 2.963)
Sodium Oxybate 6 g	-2.399	-2.397	0.9	(-4.167, -0.639)	-2.372	-2.368	2.045	(-6.714, 1.964)
Sodium Oxybate 9 g	-5.001	-5.002	0.636	(-6.246, -3.752)	-4.996	-4.994	1.528	(-8.25, -1.738)

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.

Impact of concomitant therapy

Some comparator trials allowed use of concomitant therapy, while solriamfetol trials did not allow any concomitant therapy. Concomitant therapy may overestimate the absolute treatment effect observed with a comparator and subsequently impact on the relative treatment effect generated in the ITC. Scenario analyses were explored to try to test the impact of concomitant therapies and are summarised below. See Appendix D for further details (Section D.1.5.1. and D.1.5.4 for further methods details and Section D.1.5.6. for results).

Versus sodium oxybate: Two of the three sodium oxybate studies (Xyrem, 2002 (109) and Xyrem, 2005 (111)) included a high proportion of patients using background therapies (approximately 80% of participants were using stimulants,

e.g., methylphenidate, modafinil). A scenario analysis for sodium oxybate was performed using only the study that did not include concomitant therapies (Black, 2006 (115)). Findings for relative effects of solriamfetol 150 mg were generally similar to the main analysis. When assessing the ESS outcome, the relative effect in favour of solriamfetol seen in the base case was reduced numerically (CrIs crossed zero) in the week 4 analysis (vs sodium oxybate 6 g), whereas a numeric benefit of sodium oxybate 9 g (CrIs crossed zero) in the week 8 base case analysis was overturned in the scenario. Given that this scenario included only one trial for sodium oxybate it is difficult to make any clear judgement on the true impact of concomitant therapies on the relative efficacy estimates generated by the base case ITC.

Versus pitolisant: The two pitolisant trials (Dauvilliers, 2013 (107); Szakacs, 2017 (108)) also allowed concomitant therapy for cataplexy using sodium oxybate or antidepressants; since both trials allowed concomitant therapy, a scenario analysis on pitolisant data which excluded these trials was not possible.

As such, the possibility that the use of concomitant therapies may have overestimated the absolute treatment effect observed with pitolisant and subsequently underestimated the relative treatment effect of solriamfetol generated by the ITC cannot be excluded. This highlights additional evidence for the improved efficacy of solriamfetol compared with pitolisant. This may also reflect the effect of removing concomitant therapies from comparator studies, as on days when MWT was tested in these studies, concomitant stimulants were not allowed.

B.2.9.3 Heterogeneity testing results

The SLR identified a limited number of RCTs for consideration in the ITC, wherein nearly all networks had only one trial per pairwise comparison, therefore assessment of heterogeneity could only be conducted on a small number of outcomes/timepoints where 2 or 3 trials were available for a particular treatment. For heterogeneity testing results see Appendix D, Section D.1.5.2.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

Cataplexy and use of concomitant therapy: One source of uncertainty in this analysis is the difference in cataplexy rates across the trial populations and related

use of concomitant therapy to manage narcolepsy/cataplexy symptoms. Cataplexy rates were 70% or greater in all trial arms for the two trials assessing pitolisant and in two of the three trials of sodium oxybate (107-109, 112), and in these same trials, a proportion of patients used additional concomitant therapies (i.e., in the two pitolisant trials, 35% (107) and 11% (108) of patients used sodium oxybate or antidepressants; in the two sodium oxybate trials with 100% cataplexy patients, 83% (109) and 78% (112) of patients used stimulants or modafinil). Cataplexy rates were less than 70% in all arms of trials of solriamfetol and in one of the three trials of sodium oxybate, and no concomitant therapies were allowed in these studies (75, 76, 115). A comparison of only the trials with similar rates of cataplexy as the solriamfetol trials would result in losing comparisons against sodium oxybate. It is currently unclear whether cataplexy is an effect modifier for measuring the efficacy of wake-promoting agents. Solriamfetol is not thought to affect cataplexy; pitolisant and sodium oxybate may be used for cataplexy treatment (65-67). Given the uncertainties around the effect of cataplexy on narcolepsy disease severity and comparisons of drugs that promote wakefulness and treat cataplexy, it was not possible to perform a scenario analysis to examine the effect of cataplexy in this ITC. However, to attempt to determine the effect of concomitant stimulant or modafinil use, a scenario analysis for sodium oxybate was performed using only the study that did not include concomitant therapies (115).

As described in Section B.2.9.2.5, these analyses are inconclusive for sodium oxybate, and in the absence of pitolisant trials that excluded concomitant therapy use, a potential impact on absolute treatment effect with pitolisant cannot be excluded.

Use of non-recommended dosing: A second source of bias is whether studies followed recommended clinical practice. Two trials assessing sodium oxybate did not follow recommended clinical practice for dosing (i.e., initial dose and titration) (109, 115). The recommended initial dose of sodium oxybate is 4.5 g once daily in 2 divided doses, and the dose can be increased with at least 1 week between 1.5 g dose increments (118). In Xyrem, 2002, patients randomized to sodium oxybate were not titrated onto the assigned study dose; they received a single dose (3, 6, or 9 g once daily) throughout the trial. In Black, 2006, patients assigned to sodium

oxybate were initiated on 6 g once daily sodium oxybate. Doses that are either too low (i.e., <4.5 g once daily) or initially too high (i.e., >4.5 g once daily) have the potential for low efficacy or high AEs, respectively, and therefore results from these study arms should be interpreted with caution. No adjustment was possible to correct for these non-recommended dosing arms.

Other sources of uncertainty: Other areas of uncertainty include MWT test duration, outcome timepoints, dose labelling, outcome value reporting, imputing of means and SEs, and adjustments for non-occurring events.

MWT test duration: MWT tests were performed over 20-minute and 40-minute durations. To enable comparison of solriamfetol data with comparators using the MWT20 test (i.e., sodium oxybate, modafinil), MWT20 scores were calculated through a post-hoc analysis by Jazz Pharmaceuticals censoring patient-level MWT40 scores from the TONES 2 trial. Patient-level data from TONES 1 (75) was not available to censor to 20 minutes. This decision affected the following outcomes:

- TONES 2: MWT20 at 4 weeks.

Outcome timepoints: All efficacy analyses were conducted at standardized timepoints of 4, 8, and 12 weeks (based on availability of data). An assumption was made that any outcomes assessed within 1 week of these timepoints was considered as that timepoint. For example, outcomes reported at 3 weeks would be pooled with 4-week outcomes. Any outcomes not reported at or within 1 week of 4, 8, or 12 weeks were not included in the analyses. This correction was made for the following outcomes:

- Dauvilliers, 2013: ESS (3 and 7 weeks labelled as 4 and 8 weeks, respectively).
- Szakacs, 2017: ESS, MWT40, (7 weeks labelled as 8 weeks).

For the MWT40 outcome, outcomes were reported at 4 and 12 weeks for solriamfetol (TONES 2), at 7-8 weeks for pitolisant (Dauvilliers, 2013 and Szakacs, 2017), and at 4 and 8 weeks for sodium oxybate (Xyrem, 2005). The change from baseline in MWT40 values for TONES 2 were considered sufficiently similar at 4 and 12 weeks such that either the 4- or 12-week values from TONES 2 could be used in analysis against 8-week values for pitolisant and sodium oxybate (Table 32).

Table 32. MWT40 in TONES 2 Trial

	4 weeks		12 weeks	
	MWT40 change from baseline	**SE**	**MWT40 change from baseline**	**SE**
Placebo	2.2	1.2	2.1	1.3
Solriamfetol 75 mg qd	4.7	1.2	4.7	1.3
Solriamfetol 150 mg qd	9.2	1.2	9.8	1.3

Abbreviations: MWT40, 40-minute Maintenance of Wakefulness Test; qd, once daily; SE, standard error.

To enable comparison of solriamfetol versus pitolisant and sodium oxybate for MWT, the 4-week outcomes for solriamfetol were used to compare against 7-8 week outcomes for pitolisant and sodium oxybate. The 4-week values were chosen to present the most conservative approach; in other words, comparing 12-week solriamfetol data versus 8-week pitolisant data may have been of disadvantage to pitolisant (as any efficacy changes from week 8 to week 12 of pitolisant treatment would therefore not be accounted for in the analysis). Without this assumption, it would not be possible to measure comparative efficacy in the MWT of solriamfetol versus pitolisant at any timepoint.

Safety data is reported at a single timepoint as the cumulative incidence of experiencing a treatment emergent adverse event (TEAE) throughout the course of the trial at the final study visit. Most AEs occur early in the course of treatment (e.g., within the first 1-2 weeks), resolve quickly, then diminish (see Appendix C). In other words, after 1-2 weeks on treatment, the likelihood of experiencing a TEAE is not related to treatment duration. Therefore, all safety analyses were conducted irrespective of follow-up time using safety data from the final visit.

Dose labelling: The ITC was stratified by treatment dose, therefore each node in the network represents a specific treatment and dose. For example, the comparative efficacy or safety of solriamfetol is stratified to differentiate 75 and 150 mg once daily doses. For studies which included dose titration to reach the final study dose, doses were standardized to the single dose used for at least 1 week prior to the outcome assessment. This decision affected the following outcomes:

- Ruoff, 2016: ESS outcomes at 4 weeks were labelled as 150 mg solriamfetol; ESS and MWT40 outcomes at 8 and 12 weeks were labelled as 300 mg

solriamfetol (no MWT40 reported at 4 weeks); 8 and 12 week outcomes were excluded from analysis.

- Black, 2006: ESS outcomes at 4 weeks were labelled as 6 g sodium oxybate; ESS and MWT20 outcomes at 8 weeks were labelled as 9 g sodium oxybate (no MWT20 reported at 4 weeks).

The trials for solriamfetol and sodium oxybate included stable dosing throughout the treatment period following titration. However, both trials for pitolisant (Dauvilliers, 2013 and Szakacs, 2017) included a pitolisant treatment arm that allowed patients to adjust to various doses of pitolisant (≤40 mg once daily). Outcome reporting was not stratified based on the pitolisant dose used throughout the trial. In this instance, there was no adjustment possible except to acknowledge that the dose of pitolisant used was '≤40 mg'.

Modafinil was not considered as a comparator in this ITC; therefore, modafinil study arms from any studies that assessed comparators of interest (i.e., sodium oxybate or pitolisant) were excluded from the analysis. The decision affected the following treatment arms:

- Dauvilliers, 2013: 100-400 mg once daily modafinil once daily.
- Black, 2006: sodium oxybate 6-9 g once daily + modafinil 200-600 mg once daily.

Adjusted and unadjusted outcome values: ESS and MWT outcome values in the TONES 2 trial were both reported as least squares means (i.e., adjusted) and as unadjusted means. All other studies do not specify whether the means being reported are adjusted or unadjusted. Default analysis used adjusted values from TONES 2. A sensitivity analysis was conducted using unadjusted values from TONES 2, which demonstrated no significant changes in ITC findings.

Arithmetic and geometric means: In most cases, trials did not specify whether geometric or arithmetic means were reported; however, the two pitolisant trials described some results as geometric means. As no arithmetic means were available for these outcomes, an assumption was made that geometric and arithmetic means would be sufficiently comparable for the purposes of the ITC. The ITC measures the relative effect of treatment over placebo, so the assumption that geometric means could be included is valid if both the active arm and placebo change from baseline are reported as geometric means (as is the case in the two pitolisant studies). Geometric means were reported in the following outcomes:

- Dauvilliers, 2013: ESS, MWT40.
- Szakacs, 2017: MWT40.

Trials not reporting SD/SE for change-from-baseline outcomes: For studies that did not report a change-from-baseline value but reported baseline and endpoint values, change-from-baseline values were calculated by subtracting the baseline value from the endpoint value. This calculation requires an assumption that the mean of patient-level change from baseline for any outcome is equivalent to the cohort-level baseline mean subtracted from the cohort-level endpoint mean. Standard errors were then imputed using the formula described by the Agency for Healthcare Research and Quality (Equation 1).(119)

Equation 1. Formula for calculating error of change-from-baseline value (119)

$$SD_{E,change} = \sqrt{SD^2_{E,baseline} + SD^2_{E,final} - (2\ x\ Corr\ x\ SD_{E,baseline}\ x\ SD_{E,final})}$$

$SD_{E,change}$, SD of the change-from-baseline

$SD_{E,baseline}$, SD of the baseline value

$SD_{E,final}$, SD of the endpoint value

Per this guidance, the correlation ("Corr") was defined as 0.55 for the treatment arm and 0.75 for the placebo arm (119). This correction was used in the following outcomes:

- Dauvilliers, 2013: change in ESS at 3 weeks; change in MWT40 at 8 weeks.
- Szakacs, 2017: change in ESS at 8 weeks; change in MWT40 at 8 weeks.

For outcomes in which the SD or SE were not reported at individual timepoints, it was not possible to use the Agency for Healthcare Research and Quality method to input SE. Therefore, SE values were imputed from available data for each outcome at each timepoint using guidance from the Cochrane Collaboration (120). For the placebo arm, SEs were imputed as the average of all other presented placebo SEs weighted by the number of patients in the trial arm. For all other comparators, missing SEs were imputed as the weighted average of all presented SEs across all comparators. This calculation was used for the following outcomes:

- Xyrem, 2002: change in ESS at 4 weeks.
- Xyrem, 2005: change in ESS at 4 and 8 weeks, change in MWT40 at 4 and 8 weeks.
- Black, 2006: change in ESS at 4 and 8 weeks.
- Szakacs, 2017: change in ESS at 8 weeks.

Trials reporting medians (instead of mean values): For trials reporting median values instead of means for outcomes, guidance from Hozo, 2005 was used to justify the use of medians instead of means.(121) This guidance states that, for sample sizes of 25 or more, a median is sufficiently similar to a mean. In the cases where only medians were reported, all study arms had at least 25 patients, and therefore medians were used. The assumption of medians as means was used for the following outcomes:

- Xyrem, 2002: change in ESS at 4 weeks.
- Xyrem, 2005: change in ESS at 4 and 8 weeks, change in MWT40 at 4 and 8 weeks.
- Black, 2006: change in ESS at 4 and 8 weeks.

Binary outcomes with zero responders: Analyses of binary variables with zero responders reporting the outcome (i.e., AEs) result in unstable networks with wide credible intervals. Therefore, an adjustment was made according to the NICE Technical Support Document (TSD) 2 (116). Trial arms reporting zero responders was substituted to have 0.5 responders and the sample size was increased by 1 to approximate zero responders in the input data. This substitution was required for the following outcomes:

- TONES 2: Serious AEs
- Dauvilliers, 2013: AEs leading to discontinuation
- Szakacs, 2017: Serious AEs, TEAEs leading to discontinuation
- Xyrem, 2005: Serious AEs.

Per NICE TSD 2 guidance (116), if a trial reported all treatment arms as having zero responders, that trial was excluded from that particular analysis.

B.2.10 Adverse reactions

Across the entire clinical development programme for solriamfetol, 1,605 people have been exposed to solriamfetol (including the unlicensed 300 mg dose) as of 8 February 2018), including patients with narcolepsy, OSA, or major depressive disorder, and healthy subjects.

In the clinical trial program for solriamfetol, 321[n] unique patients with narcolepsy were treated with solriamfetol (all doses, including the 300 mg dose): 172 were exposed to solriamfetol for at least 6 months, and 95 for at least 12 months. During long term treatment in TONES 5 the mean (SD) treatment exposure in the overall combined solriamfetol population (Safety Population, including the 300 mg dose) during the open label phase was [redacted] or approximately [redacted], and in the narcolepsy population was [redacted].

An overview of AE data from the two Phase 3 trials that enrolled patients with narcolepsy and EDS is provided by treatment arm for the Safety Populations in TONES 2 (Table 33) and TONES 5 (Table 34). AE data from the supporting Phase 2 study (TONES 1) has also been provided as these data have been included in the ITC Table 35.

A safety overview, including narratives of common AEs, serious AEs, discontinuations due to AEs, and AEs of special interest is also provided. Where possible this narrative is based on the two Phase 3 narcolepsy trials (TONES 2 and

[n] For TONES 5, patients were eligible for inclusion if they had completed previous studies, including TONES 2 and TONES 1, hence some patients appear in the safety populations of these parent studies as well as TONES 5; as such the sum of the individual safety populations enrolled in all narcolepsy trials is larger than the number of unique patients who received solriamfetol (N=321).

TONES 5). Broader observations from pooled safety data, as submitted for European Medicines Agency (EMA) marketing authorisation and including evidence from the wider evidence base (for example, observations from the broader clinical trial programme) are also included, where appropriate.

All AEs are [redacted] (for TONES 5 this meant AEs that began or worsened during TONES 5, not the parent study).

B.2.10.1 Safety overview

- Analysis of AEs showed that solriamfetol in the proposed therapeutic dose range for narcolepsy (75 to 150 mg) [redacted] Among the [redacted] patients with narcolepsy (321 unique patient exposures) treated with solriamfetol (including the unlicensed 300 mg dose) during TONES 2 and 5, there were no deaths and serious AEs were reported in 7 patients.
- The majority of AEs experienced in patients with narcolepsy were classified as mild or moderate (TONES 2: solriamfetol 75 mg, [redacted], solriamfetol 150 mg, [redacted]; TONES 5: 88.2% including the unlicensed solriamfetol 300 mg dose).
- The incidence of AEs leading to discontinuation of solriamfetol and/or study withdrawal was dose-related with a mean across all doses in TONES 2 of 5.1%; mean incidence for the 75 and 150 mg doses were 1.7% and 5.1%, respectively (Table 33). In TONES 5 the incidence was 10.2% across the combined dose group (Table 34), however 56.8% of AEs occurred within the first 4 weeks of treatment.
- There was no evidence to suggest the late emergence of AEs with long-term solriamfetol treatment in TONES 5 (including with the unlicensed 300 mg dose).
- The AE profile of solriamfetol is consistent with the expected pharmacology of a DNRI – the class of drug to which solriamfetol belongs – and the well characterised pharmacokinetic characteristics of solriamfetol, and was consistent across all populations studied in the trial programme.
- In general, AEs are dose related (with the unlicensed 300 mg dose having the greatest rates of AEs) and appear to be reversible. The nature of the AEs is

such that they can be detected, monitored, and managed with routine measures and treatments used in clinical practice, addressed through dose reduction or drug discontinuation, if needed, and are described in the SmPC[redacted]

Table 33. TONES 2: Summary of AEs (Safety Population)

	Patients, n (%)		
		Solriamfetol	
	Placebo N=59	75 mg N=59	150 mg N=59
Any AE	27 (45.8)	34 (57.6)	47 (79.7)
Any treatment-related AE†	[redacted]	[redacted]	[redacted]
Serious AE	0	0	1 (1.7)
Any treatment-related serious AEs†	[redacted]	[redacted]	[redacted]
AE leading to study drug and study discontinuation	1 (1.7)	1 (1.7)	3 (5.1)
Deaths	0	0	0
AEs occurring in ≥5% of patients			
Headache	3 (5.1)	6 (10.2)	14 (23.7)
Nausea	1 (1.7)	3 (5.1)	6 (10.2)
Decreased appetite	1 (1.7)	5 (8.5)	5 (8.5)
Nasopharyngitis	3 (5.1)	5 (8.5)	8 (13.6)
Dry mouth	2 (3.4)	3 (5.1)	4 (6.8)
Anxiety	1 (1.7)	1 (1.7)	3 (5.1)
Diarrhoea	1 (1.7)	2 (3.4)	3 (5.1)
Dyspepsia	0	1 (1.7)	2 (3.4)
Dizziness	2 (3.4)	2 (3.4)	1 (1.7)
Fatigue	0	0	2 (3.4)
Weight decreased	0	1 (1.7)	1 (1.7)
Insomnia	0	2 (3.4)	0
Upper respiratory tract infection	1 (1.7)	1 (1.7)	4 (6.8)
Heart rate increased	0	0	0
Constipation	1 (1.7)	3 (5.1)	1 (1.7)
Influenza	3 (5.1)	2 (3.4)	1 (1.7)
Weight increased	3 (5.1)	2 (3.4)	0

Abbreviations: AE, adverse event; CSR, clinical study report; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

[redacted]

Source: Thorpy 2019 (77); CSR Table 31 and Table 35 (76).

Table 34. TONES 5: Summary of AEs across entire study, including the unlicensed 300 mg dose (Safety Population)

	Patients receiving solriamfetol (all doses), n (%)	
	Overall N=643	**Narcolepsy N=226**
Any AE	482 (75.0)	169 (74.8)
Any treatment-related AE†	[redacted]	[redacted]
Serious AE	27 (4.2)	6 (2.7)
Any treatment-related serious AEs†	5 (0.8)	1 (0.4)
AE leading to study drug or study discontinuation	59 (9.2)	23 (10.2)
Deaths	1 (0.2)‡	0
AEs occurring in ≥5% of patients (in combined solriamfetol group for any indication)		
Headache	71 (11.0)	31 (13.7)
Nausea	57 (8.9)	26 (11.5)
Nasopharyngitis	54 (8.4)	19 (8.4)
Insomnia	51 (7.9)	16 (7.1)
Dry mouth	47 (7.3)	14 (6.2)
Anxiety	46 (7.2)	21 (9.3)
Decreased appetite	32 (5.0)	18 (8.0)
Upper respiratory tract infection	32 (5.0)	10 (4.4)

Abbreviations: AE, adverse event; CSR, clinical study report; OSA, obstructive sleep apnoea; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

[redacted]

‡ Due to sepsis in a patient with OSA; OSA data is not presented in this submission.
Source: Malhotra 2019 (85).

Table 35. TONES 1: Summary of AEs after 4 weeks of treatment with solriamfetol 150 mg (Safety Population)

	Solriamfetol 150 mg/day n=44	Placebo n=49
Any AE	27 (61.4)	29 (59.2)
Any treatment-related AE†	NR	[redacted]
Serious AE	1 (2.3)	0
AE leading to study drug or study discontinuation	2 (4.5)	2 (4.1)
Deaths	0	0
AEs occurring in ≥5% of patients		
Headache	5 (11.4)	5 (10.2)
Nausea	1 (2.3)	3 (6.1)
Diarrhoea	2 (4.5)	3 (6.1)
Insomnia‡	[redacted]	[redacted]
Decreased appetite	4 (9.1)	0
Anxiety	4 (9.1)	0
Irritability	2 (4.5)	1 (2.0)
Palpitations	3 (6.8)	1 (2.0)
Dizziness	1 (2.3)	1 (2.0)
Agitation	3 (6.8)	0
Bruxism	3 (6.8)	0

Abbreviations: AE, adverse event; CSR, clinical study report; NR, not reported; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Data presented as n (%)
All AEs are treatment emergent AEs, defined as AEs that either began after the first dose of study drug [redacted]
‡ Preferred term: insomnia not otherwise specified.
Source: Ruoff 2016 (75); CSR (83).

B.2.10.2 AE profile in Phase 3 placebo-controlled trials

- Based on the TONES 2 12-week, placebo-controlled study, more patients experienced at least one AE with solriamfetol 75 and 150 mg doses (57.6% and 79.7%,respectively) than placebo (45.8%) (Table 33).
- The most frequent AEs[o] that had a higher incidence with solriamfetol than placebo included (Table 33):
  - Solriamfetol 75 mg: headache (10.2%), nausea (5.1%), decreased appetite (8.5%), nasopharyngitis (8.5%), dry mouth (5.1%).
  - Solriamfetol 150 mg: headache (23.7%), nausea (10.2%), decreased appetite (8.5%), nasopharyngitis (13.6%), dry mouth (6.8%).
- The majority of these AEs occurred within the first 2 weeks of initiating treatment and resolved for the majority of patients with a median duration of less than 2 weeks.
- One patient in the solriamfetol arm (solriamfetol 150 mg) had two serious AEs (non-cardiac chest pain, anxiety) that were not considered by the investigator to be related to study medication; the patient continued the study without recurrence of the events.
- AEs[o] that led to study drug and/or study discontinuation were reported in 1.7 and 5.1% of the solriamfetol 75 and 150 mg groups, respectively, compared with 1.7% in the placebo arm.

B.2.10.3 Adverse events of special interest

B.2.10.3.1 Insomnia

- Solriamfetol is a wake promoting agent, intended to treat EDS, and events of insomnia occurred in patients receiving solriamfetol in early clinical studies. Accordingly, AEs of insomnia were examined further in the clinical trial programme.

[o] Five most common AEs reported in ≥5% of patients across any treatment group including the 300 mg dose

- In TONES 2, insomnia was reported in 3.4 and 0.0% of patients receiving solriamfetol 75 and 150 mg, respectively) compared with 0.0% of the placebo arm; no patients discontinued due to insomnia.
- Events of insomnia across TONES 2 and 5 were [redacted], and [redacted]osing; few events led to study withdrawal (n=0 in TONES 2; n=4 in TONES 5).
- Furthermore, an exploratory endpoint in TONES 2 assessed overnight polysomnography (PSG) measurements, including total sleep time, number of awakenings, or wake after sleep onset. Solriamfetol did not have an effect on sleep architecture, and no clinically significant changes in polysomnography parameters were observed.

B.2.10.3.2 Depression and suicidal ideation

- Depression is a common comorbidity in narcolepsy, and patients with narcolepsy are almost twice as likely to report depression compared with subjects without narcolepsy (44). The potential for depression and suicidality was explored in Phase 3 studies with the validated Columbia-Suicide Severity Rating Scale (C-SSRS) [redacted].
- However, in TONES 2, AEs associated with depression (depression, depressed mood, depressive symptoms, dysthymic disorder, or crying) [redacted] for solriamfetol 75 mg and [redacted] for solriamfetol 150 mg, compared with [redacted] in the placebo arm).
- In addition, the C-SSRS did not reveal any clear pattern of suicidality related to solriamfetol across TONES 2 and 5.

B.2.10.3.3 Risk for cardiovascular events, and blood pressure and heart rate increases

- In TONES 2, there were small mean changes in blood pressure (BP) and heart rate (HR) from baseline to week 12 (averages across the day from pre-dose to 9 hours post-dose); these effects were dose-dependent (Table 36).
  - The effects on BP and HR from baseline to week 8 using 24 hour ambulatory monitoring were similar to the effects observed during the days on which MWT was performed (Table 36).

Table 36. TONES 2: changes in BP or HR (Safety Population)

	Placebo N=59	Solriamfetol 75 mg N=59	Solriamfetol 150 mg N=59
Change from baseline to week 12, as measured on MWT days*			
n	50	48	49
HR, bpm	0.5 (6.7)	0.6 (6.6)	2.5 (4.7)
Systolic BP	0.6 (8.1)	0.3 (6.8)	1.2 (7.4)
Diastolic BP	-0.6 (5.2)	1.0 (4.4)	1.4 (4.9)
Change from baseline to week 8, as measured by ambulatory BP monitoring†			
n	50	46	46
HR, bpm	-0.6 (7.0)	1.0 (8.0)	0.7 (7.1)
Systolic BP	-0.3 (9.3)	1.8 (6.5)	-0.5 (5.5)
Diastolic BP	-0.1 (7.2)	1.4 (5.1)	0.4 (4.5)

Abbreviations: BP, blood pressure; bpm, beats per minute; HR, heart rate.
Data presented as mean (SD) unless otherwise stated. Analysis conducted on patients with non-missing values.
*Vital signs averaged across pre-dose to 9 hours post-baseline
†Vital signs matched by time point at baseline and week 8.

- TONES 5 showed no clinically relevant changes from baseline of the parent study for systolic or diastolic BP during the open-label phase and there were no apparent trends to suggest that BP or HR would increase over time during the 40–52 weeks of solriamfetol treatment (including the unlicensed 300 mg dose).
  - [redacted] patients with narcolepsy experienced an AE of hypertension in TONES 2 or in TONES 5.
- [redacted].
- The most common cardiovascular AE in patients receiving solriamfetol in a placebo-controlled setting (TONES 2, overall rate of AEs including the unlicensed 300 mg dose) was [redacted] however [redacted] patients were receiving the unlicensed 300 mg dose and there were [redacted] in the solriamfetol 75 or 150 mg dose.
  - There were [redacted] cardiovascular AEs in patients receiving solriamfetol 75 mg.
  - Incidence of cardiovascular AEs in the solriamfetol 150 mg arm included [redacted] non-cardiac chest pain (n=2, 3.4%), [redacted]
- Serious AEs of a cardiovascular or potentially cardiovascular nature were uncommon. One patient in TONES 2 reported a serious AE of non-cardiac

chest pain (solriamfetol 150 mg), but this was not considered related to study drug and the subject completed the study. In TONES 5 there were no serious AEs of a cardiovascular or potentially cardiovascular nature in patients with narcolepsy.

- In light of these effects, appropriate precautions for use are listed in the SmPC, including periodic monitoring of BP and HR (prior to initiation and during treatment), controlling pre-existing hypertension prior to initiating treatment, and avoiding use of solriamfetol in patients with unstable cardiovascular disease, serious heart arrhythmias and other serious heart problems. This is broadly similar to other therapies used to treat narcolepsy.

B.2.10.4 Abuse potential

There is a significant unmet need for a pharmacotherapy that has robust and sustained efficacy in treating EDS in OSA, balanced with low potential for AEs and low potential for abuse. As a wake-promoting agent, solriamfetol has been thoroughly tested for its abuse potential; preclinical data, combined with the results of a human abuse potential study (Study 14-001 (122), in which solriamfetol was compared to placebo and the amphetamine stimulant phentermine), indicated that solriamfetol has low potential for abuse.

B.2.10.5 Other findings

B.2.10.5.1 Withdrawal effects

During TONES 5, in which patients on a stable dose of solriamfetol (including the 75, 150 and unlicensed 300 mg dose) were then randomised to either continue solriamfetol or switch to placebo, there was no evidence of rebound hypersomnia or withdrawal effects after abrupt discontinuation of solriamfetol in the placebo group.

B.2.10.6 Safety conclusion

The clinical experience with solriamfetol demonstrated solriamfetol (all doses, including the unlicensed 300 mg dose) to be consistently well tolerated in short- (12 weeks) and long-term (40–52 weeks) trials in patients with narcolepsy and EDS.

[redacted]

[redacted]AEs are generally dose related in frequency with the highest rates in the 300 mg arms (unlicensed), mild or moderate in severity, short-lived and resolved within 2 weeks for the majority of patients[redacted] (see Appendix C).

[redacted].

B.2.11 Ongoing studies

There are no new data anticipated from the completed studies described in Section B.2.2. There is one ongoing study of solriamfetol in patients with narcolepsy (Study 15-005; NCT02806908) but the date of availability of data from this study is not established at the time of submission.

B.2.12 Innovation

Patients with EDS due to narcolepsy who have failed first-line modafinil may subsequently be prescribed Schedule 2, unlicensed treatments, or may have difficulties accessing expensive medicines due to local variation in funding and guidelines (e.g. individual funding requests). Methylphenidate is unlicensed in narcolepsy and (in the absence of RCT data) dexamfetamine achieved its MHRA licence based on expert clinical opinion, and there are no RCTs which demonstrate the clinical benefit of methylphenidate or dexamfetamine in treating the EDS due to narcolepsy. To date, only one published study has reported on the cost-effectiveness of a treatment for narcolepsy (Lanting, 2014 for sodium oxybate) however the conclusion for the study was the sodium oxybate would not represent good value for money for the NHS; furthermore, this treatment is not specifically treating EDS due to narcolepsy. None of the treatments defined in the company decision problem has received a positive recommendation from UK HTA bodies, including NICE.

The clinical trial programme for solriamfetol demonstrates the efficacy of solriamfetol in reducing sleepiness and improving wakefulness in patients with EDS due to narcolepsy. In addition to its clinical efficacy in treating EDS, solriamfetol delivers additional health-related benefits that are not captured in the quality adjusted life year (QALY) calculation (presented in Section B.3).

Solriamfetol has a selective mechanism of action

Solriamfetol acts as a selective dual reuptake inhibitor of the wake-promoting neurotransmitters dopamine and norepinephrine (123), making its mechanism distinct from other pharmacological interventions currently used in narcolepsy. Solriamfetol is distinguished mechanistically from the amphetamine stimulants dexamfetamine and methylphenidate by its lack of release of monoamines (123). It is hypothesised that these mechanistic characteristics account for the robust wake-promoting effects of solriamfetol and the lack of rebound hypersomnia observed upon solriamfetol withdrawal (77).

Solriamfetol is not a substrate or inhibitor of any of the major CYP enzymes, with the exception of weak inhibition of CYP2D6, and is not an inhibitor of renal transporters, with the exception of weak inhibition of OCT2 and MATE1. As such, clinically

relevant pharmacokinetic drug interactions are unlikely to occur in patients receiving solriamfetol. Furthermore, solriamfetol is excreted unchanged in urine and has minimal hepatic metabolism thus hepatic impairment is not expected to have an impact on solriamfetol elimination. Per the solriamfetol licence, no dose adjustment is required for mild renal impairment, and reduced dosing is recommended in moderate and severe renal impairment (see Appendix C).

Solriamfetol has low abuse potential

Many stimulant drugs used for the treatment of narcolepsy, including modafinil and methylphenidate (unlicensed in narcolepsy), have an established addictive profile (61). As a wake-promoting agent, solriamfetol has been thoroughly tested for its abuse potential; preclinical data, combined with the results of a human abuse potential study (Study 14-001, in which solriamfetol was compared to placebo and the amphetamine stimulant phentermine (122)), indicated that solriamfetol has low potential for abuse. Data from the TONES 5 extension study demonstrated that following long-term (up to 6 months) solriamfetol use, withdrawal of treatment did not result in withdrawal-related adverse effects or rebound hypersomnia (see Section B.2.6.3.3.1). The licences for modafinil, sodium oxybate, dexamfetamine, and methylphenidate (unlicensed in narcolepsy) contain warnings on the potential for dependence with long-term use and state that patients should be carefully monitored for signs of abuse or dependence, during treatment and after treatment discontinuation (62-66); in contrast there are no such warnings in the licence for solriamfetol (see Appendix C).

Solriamfetol offers convenient dosing and extended duration of effect

Solriamfetol is a once daily, oral treatment, taken with or without food upon awakening. The only other treatment for narcolepsy with once daily dosing is pitolisant, however pitolisant may not be suitable for all patients as it must be taken with food at breakfast (66). Both IR and MR formulations of methylphenidate (unlicensed in narcolepsy) are available, however even using MR tablets, patients may need to split their dose across the day to maintain wakefulness (62). This is also the case for some patients taking modafinil and dexamfetamine, who may find that the treatment effects wear off in the afternoon and the patient requires an additional dose to boost wakefulness (124, 125). In patients who do not respond to 200 mg

modafinil dosing, doses of up to 400 mg taken as a single or divided dose may be required (65) and there is evidence that patients using a 400 mg split dosing regimen have greater wakefulness in the evening than those with a once daily regimen (125).

Sodium oxybate is taken at night in two divided doses: the first dose should be taken at bedtime and the second dose should be taken 2.5–4 hours after the first dose. Patients should take both doses while in bed and lie down immediately after dosing as sodium oxybate may cause them to fall asleep abruptly without first feeling drowsy; patients are directed to prepare both doses before bedtime. Prior to ingestion, each dose of sodium oxybate should be diluted with approximately 60 mL of water (diluting the oral solution in water; doses can be used for ≤24 hours after preparation) (66, 126). Although patients may feel better within a few days, it can take up to 2 months to observe a clinically meaningful response up to 8–12 weeks of regular dosing to achieve with maximum optimal response achieved in most patients after a longer period in terms of EDS (110).

The solriamfetol dosing regimen is therefore less disruptive and more convenient than its comparators, which may require food/meal restrictions, multiple doses per day, preparation of doses by dilution, or waking up during the night (63-68). In addition to the convenient once daily dosing, the beneficial effects of solriamfetol in treating EDS are sustained throughout the day, which offers an advantage over its comparators. Evidence from clinical trials shows that solriamfetol effects on EDS are observed within 1 week post-treatment thus solriamfetol can deliver rapid reduction of the burden of EDS due to narcolepsy (see Section B.2.6.1.5).

Solriamfetol treatment does not modify sleep architecture

Insomnia is a common and expected side effect of stimulant treatments based on the pharmacology of these drugs (65-67). Clinical trial data demonstrated that solriamfetol does not impact sleep architecture, with minimal changes detected using PSG measurements, including total sleep time, number of awakenings and wake time after sleep onset, compared with placebo; in addition, solriamfetol treatment was associated with low rates of insomnia (2.8%) (see Section B.2.10.3.1). By comparison, abrupt withdrawal of dexamfetamine can be associated with insomnia,

changes in EEG during sleep, and/or extreme fatigue (63, 65, 66), indicating that long-term treatment with this comparator may modify sleep architecture.

Solriamfetol improves patient productivity at work and outside work

People with EDS unrelated to an underlying condition experience significantly greater impairment in work productivity and activities outside work, compared with people without EDS; furthermore, people with EDS as a symptom of an underlying condition such as narcolepsy are more impaired than those without an underlying condition (127). EDS associated with narcolepsy can have a substantial negative impact on a patient's professional life, and impair their ability to perform daily activities (44). The impact of solriamfetol on work productivity and activity impairment was assessed in TONES 2 and TONES 5, using the WPAI:SHP questionnaire. In TONES 2, after 12 weeks of treatment solriamfetol 150 mg decreased rates of presenteeism (impairment while working), overall work impairment, and activity impairment outside of work compared with placebo (all nominal $p<0.05$) (see Section B.2.6.1.9). Long-term treatment with solriamfetol (combined arm, including unlicensed 300 mg dose), as explored in TONES 5, led to reduced rates of presenteeism (impairment while working), overall work impairment and activity impairment outside of work by at least 25% from baseline in patients with narcolepsy; these improvements were observed by week 14 and maintained throughout the duration of the study (up to 52 weeks) (see Section B.2.6.3.2.4). This impact on work productivity may provide an additional impact on quality of life, if it could help patients into employment (see Appendix A), who were previously unable to work due to their condition, and/or increase the earning potential of those in low paid jobs.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The totality of evidence across the Phase 3 clinical trial programme for solriamfetol in narcolepsy (TONES 2 and TONES 5) shows that the effects of solriamfetol treatment on EDS due to narcolepsy are clinically meaningful, rapid in onset (within 1 hour of dosing), and are maintained long-term (over at least 6 months of treatment[p]). In both trials, the clinical benefit of solriamfetol was demonstrated using validated objective and subjective outcome measures, including ESS, MWT, PGI-c or CGI-c. The Phase 2 TONES 1 study provides additional evidence that is supportive of the Phase 3 programme. These efficacy results combined with the well-characterised safety profile of solriamfetol demonstrate its potential to improve the treatment landscape for patients with EDS due to narcolepsy.

B.2.13.1.1 TONES 2: Phase 3 comparative efficacy over 12 weeks

TONES 2 is the pivotal RCT providing evidence of comparative efficacy of solriamfetol compared with placebo in adult patients with EDS due to narcolepsy (diagnosed according to the ICSD-3 or Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-5] criteria). Patients had to have EDS and an inability to stay awake as demonstrated by a baseline ESS score ≥10 and a baseline mean sleep latency of <25 minutes (the mean of the first four trials of a five-trial MWT), respectively.

Solriamfetol reduced EDS and improved wakefulness as demonstrated by, respectively, a significant decrease in subjective ESS score from baseline to week 12 for solriamfetol 75 and 150 mg (LS mean difference vs placebo -2.2 and -3.8, respectively; both $p<0.05$) and significant increases in the duration of objective MWT mean sleep latency score from baseline to week 12 for the solriamfetol 150 mg dose (LS mean difference vs placebo 7.7 minutes; $p<0.0001$). The study was not powered

p Improvements in ESS scores were maintained for at least 6 months and up to 1 year.

for the 75mg dose, however numerical improvements in MWT for the 75 mg dose were observed (LS mean difference vs placebo 2.6 minutes; p>0.05).

Improvements in ESS versus placebo were observed from week 1 (the first measurement time point) (p<0.05 for 150 mg, numerical improvement for 75 mg). Normal ESS (≤10) scores (Table 6) were achieved by 30.5% and 40.0% of patients receiving solriamfetol 75 and 150 mg, respectively, compared with 15.5% in the placebo group.

Evaluation of MWT demonstrated that patients receiving solriamfetol 75 mg and 150 mg doses achieved significant (p<0.05) improvements at week 1. MWT sleep latency ranges from 0–40 minutes (lower scores indicating a great inability to stay awake), with an MWT of 19.4 minutes reported as the lower limit of normal (Table 6). After 12 weeks of treatment, mean MWT scores were [redacted] for placebo, solriamfetol 75 mg and solriamfetol 150 mg, respectively, compared with baseline MWT scores of [redacted] respectively, indicating a dose-dependent trend towards the lower limit of normal wakefulness for patients receiving solriamfetol. An assessment of sleep latency across five separate MWT tests staggered through the day (week 12) showed that the effects of solriamfetol were rapid in onset (within 1 hour after dosing) and sustained throughout the day, supporting convenient, once-daily dosing. Although some outcome measures did not reach significance at the 75 mg dose at week 12 (e.g. MWT), solriamfetol may be titrated from a starting dose of 75 mg in patients with narcolepsy to an effective and tolerated dose, up to a maximum of 150 mg.

The improvements in the co-primary outcomes of ESS and MWT were associated with improvements in the patient's overall condition, as reported by both the patient (using PGI-c) and the clinician (using CGI-c). Patient QoL scores were also improved, as measured using the FOSQ-10 and SF-36v2; using the FOSQ-10 disease specific questionnaire, solriamfetol 150 mg delivered significant improvements compared with placebo in patient functioning at weeks 1 and 8, with numerical improvements observed at week 12. Improvements observed with SF-36v2 were more limited, with EQ-5D showing no meaningful trends. At baseline, [redacted] of patients in TONES 2 had utility scores=1, and therefore reported no disutility due

to their narcolepsy. The lack of meaningful trends in EQ-5D scores in the narcolepsy population is of uncertain cause. Given the substantial negative impact that narcolepsy has on QoL (see Section B.1.3), 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. Further discussion on the suitability of EQ-5D in the narcolepsy population and relevance to economic modelling is discussed in Section B.3.4.

TONES 2 evaluated the impact of solriamfetol on work productivity and activity impairment using the WPAI:SHP. After 12 weeks of treatment, solriamfetol 150 mg decreased the rates of presenteeism (impairment while working), overall work impairment, and activity impairment outside of work (all nominal $p<0.05$).

B.2.13.1.2 TONES 1: Supporting Phase 2 comparative efficacy over 12 weeks

The comparative evidence from the Phase 2 TONES 1 study is consistent with that observed in the Phase 3 TONES 2 study and supports the comparative efficacy of solriamfetol compared with placebo in adult patients with EDS due to narcolepsy. Solriamfetol 150 mg/day for 4 weeks significantly reduced sleepiness and increased the ability to maintain wakefulness in patients with narcolepsy, with and without cataplexy. The results from TONES 1 demonstrated that at solriamfetol 150 mg/day, patients achieved significant improvements in EDS by week 4.

B.2.13.1.3 TONES 5: Long-term maintenance of efficacy

TONES 5 is the pivotal long-term open-label study demonstrating the efficacy and safety of solriamfetol (combined arm, including the unlicensed 300 mg dose) for up to 1 year. Adult patients with narcolepsy or OSA who had previously completed a clinical trial for solriamfetol in EDS were enrolled; for patients with narcolepsy these trials included TONES 2, as well as completed or ongoing Phase 2 studies (TONES 1, ADX-N05 201, or 15-005). The study also included a 2-week placebo-controlled randomised-withdrawal phase after at least 6 months of treatment to assess the effects of discontinuing solriamfetol.

In the open-label phase, TONES 5 demonstrated the long-term maintenance of efficacy with continued solriamfetol treatment (up to 52 weeks; mean duration of

treatment [redacted] for all doses including the unlicensed 300 mg dose). During the open-label phase, there was an improvement in mean ESS scores within 2 weeks of treatment (the first measurement time point), maintained for up to 52 weeks, indicating a sustained improvement in EDS; this effect was apparent across the combined solriamfetol dose group, and for the 75 and 150 mg doses. Solriamfetol treatment (including the unlicensed 300 mg dose) also improved patient QoL as measured using the FOSQ-10, EQ-5D-5L and SF-36v2, although improvements were most apparent on the FOSQ-10. Patients had numerical improvements from the first post-treatment time point through to the final evaluation indicating that in addition to the effect on ESS, solriamfetol-induced improvements in QoL are maintained in the long-term with continued treatment. Furthermore, long-term treatment with solriamfetol, led to a minimum 25% reduction in presenteeism (impairment while working), overall work impairment and activity impairment outside of work in patients with narcolepsy (as measured using the WPAI:SHP).

B.2.13.1.4 TONES 5: Reversal of effect following solriamfetol discontinuation

In the 2-week randomised-withdrawal phase of TONES 5, designed to test the effects of solriamfetol discontinuation on EDS, a proportion of patients were randomised to placebo or continued solriamfetol treatment after approximately 6 months of solriamfetol open-label treatment. During this phase, patients randomised to solriamfetol (including the unlicensed 300 mg dose) remained improved, whereas patients randomised to placebo worsened during the 2 week withdrawal period (LS mean difference of [redacted] in patients with narcolepsy; [redacted]). Analysis of ESS scores for patients receiving placebo indicated a worsening of EDS beyond the upper limit of normal (ESS ≤10; Table 6), but without exceeding baseline scores and thus indicating no evidence of rebound hypersomnia. Worsening of EDS in response to solriamfetol treatment discontinuation was associated with [redacted] as measured using the FOSQ-10 [redacted] or solriamfetol [all doses] vs placebo at the end of withdrawal phase in the overall and narcolepsy populations).

B.2.13.1.5 Safety

The clinical experience with solriamfetol has demonstrated it to be consistently well tolerated in both short-term (12 weeks) and long-term (40–52 weeks) trials of patients with narcolepsy, as well as more broadly in patients with OSA or major depressive disorder, and healthy subjects. AEs have been well characterised and are consistent with the pharmacology of the drug. In general AEs are dose-related, with highest rates associated with the 300 mg doses (which will not be licensed), and appear to be reversible, mainly within 2 weeks of onset. The nature of the AEs is such that they can be detected, monitored, and managed with routine measures and treatments used in clinical practice, addressed through dose reduction or drug discontinuation, if needed, and are described in the SmPC (see Appendix C).

In TONES 2, more patients with narcolepsy receiving solriamfetol experienced at least one AE (75 mg, 57.6%; 150 mg, 79.7%) compared with placebo (45.8%). The most frequent AEs (≥5% of patients) included headache, nausea, decreased appetite, nasopharyngitis, and dry mouth (Table 33). AEs that led to study drug and/or study discontinuation were reported in 1.7 and 5.1% of the solriamfetol 75 and 150 mg arms, respectively compared with 1.7% in the placebo arm. There was no evidence to suggest the late emergence of AEs with long-term administration of solriamfetol during TONES 5, nor of rebound hypersomnia or withdrawal effects due to abrupt discontinuation of solriamfetol.

AEs of special interest including insomnia, suicidal ideation and risk for cardiovascular events were assessed during the clinical trial programme. As a wake promoting agent the potential to cause insomnia was monitored. However, rates of insomnia reported during 12 weeks of treatment in TONES 2 were low, were mild or moderate in severity, and generally resolved with dose reduction or without change to dosing; few cases of insomnia led to study drug withdrawal (n=0 in TONES 2; [redacted] in TONES 5). Furthermore, sleep architecture appeared unaffected versus placebo, as determined by overnight PSG measurements of total sleep time, number of awakenings, or wake after sleep onset.

Depression is a common comorbidity in narcolepsy. Occurrence of depression and the risk of suicidality were therefore assessed; AEs associated with depression were

uncommon, and using the C-SSRS, no pattern of suicidality related to solriamfetol across TONES 2 and 5 was revealed.

Minimal mean increases in BP and HR were apparent from baseline to 12 weeks of solriamfetol treatment in TONES 2; the effects on BP and HR were dose dependent and were greatest in the 300 mg dose; evidence from TONES 5 (including data for the unlicensed 300 mg dose) did not show any apparent trends to suggest that BP or HR would increase over time during long term treatment for up to 52 weeks. Cardiovascular AEs, including palpitations, non-cardiac chest pain, BP increase and tachycardia occurred at [redacted] and there were no cases of HR increase in TONES 2 for patients receiving solriamfetol 75 or 150 mg. One serious AE of a cardiovascular or potentially cardiovascular nature occurred in TONES 2 (solriamfetol 150 mg arm), but was considered unrelated to solriamfetol treatment; long term treatment in TONES 5 did not result in any serious cardiovascular AEs.

A number of treatments currently used to treat EDS in patients with narcolepsy have warnings related to abuse potential (62-66). As a wake-promoting agent, solriamfetol has been thoroughly tested for its abuse potential. Preclinical data, combined with results from a human abuse-potential study (Study 14-001, that compared solriamfetol with placebo and the amphetamine stimulant phentermine (122)), indicate that solriamfetol has low potential for abuse.

B.2.13.1.6 Indirect evidence for solriamfetol in EDS

In the absence of direct evidence for solriamfetol and comparators of interest, an ITC was conducted to elicit estimates of relative effectiveness. The clinical SLR (see Section B.2.1) sought evidence for inclusion in the ITC for dexamfetamine, methylphenidate, sodium oxybate and pitolisant, in line with the company decision problem and anticipated positioning of solriamfetol in UK clinical practice.

The clinical SLR (described in Section B.2.1 and Appendix D) shows there is a general paucity of evidence available supporting treatments used in narcolepsy and which could subsequently be utilised in the ITC; no ITC-appropriate evidence was identified for dexamfetamine or methylphenidate, while pitolisant analyses had to be

restricted to combined dose analyses, in the absence of effectiveness estimates stratified by dose.

In the base-case analysis of ESS, solriamfetol 150 mg was associated with a similar beneficial impact on EDS versus pitolisant (≤40 mg; estimates stratified by pitolisant dose are not available from pitolisant trials). Compared with sodium oxybate, solriamfetol 150 mg demonstrated improvements over the 3 and 4.5 g doses (CrIs did not cross zero), numerical improvements over the 6 g dose (CrIs crossed zero), and numerical deficits to the highest 9 g dose (CrIs crossed zero).

Outcomes from the ESS analysis were subsequently utilised in the current economic model described in Section B.3.2.

B.2.13.1.7 Conclusion

Considering the clinical evidence overall, solriamfetol as a wake-promoting agent combines a rapid onset of action and a robust and durable efficacy profile that is maintained with long-term administration, and has a low potential for abuse and a well-characterised safety profile that can be monitored and managed through routine clinical practices.

B.2.13.2 Strengths and limitations of the clinical evidence base for the technology

Study design

In the Phase 3 trial programme for EDS in narcolepsy, TONES 2 and TONES 5 were large, multinational and methodologically robust trials, that used validated well-recognised outcome measures to assess the efficacy of solriamfetol for treating EDS in patients with narcolepsy (TONES 2) or patients with narcolepsy or OSA (TONES 5).

TONES 2 was a multicentre, double-blind, randomised, placebo-controlled study, representing the gold standard in clinical evidence. TONES 5 was a long-term, non-comparative, open-label extension study; although the study was not randomised, all patients had previously completed a Phase 2 (TONES 1, Study 15 004, 15-005, or ADX-N05-201) or Phase 3 (TONES 2–4) study of solriamfetol, all of which were double-blind, randomised, placebo-controlled studies (with the exception

of TONES 4). In addition to the open-label phase, TONES 5 included a randomised, placebo-controlled, double-blind withdrawal phase, which was added as a protocol amendment at the request of the Food and Drug Administration (FDA), to demonstrate the impact of solriamfetol withdrawal after ≥6 months of treatment. As a supporting Phase 2 study, TONES 1 was a multicentre, methodologically robust, placebo-controlled trial to assess the safety and efficacy of solriamfetol, and supports the evidence provided for TONES 2.

Study populations

The baseline demographics and disease-specific characteristics were similar across all three trials (TONES 2, TONES 5 and TONES 1), well-balanced between the treatment groups in each trial, and there were no unexpected differences between arms in the rates of drop-out or discontinuation.

Suitability of the trial comparator

The inclusion of a placebo control group in TONES 2 (and TONES 1) was used to provide a robust assessment of the efficacy and safety of solriamfetol as a new investigational medicinal product. The use of a placebo control is aligned with guidance on study design from the FDA which states that placebo controlled studies allow the effect of the new agent to be distinguished from 'placebo effects' (128). The FDA guidance further states in the absence of a placebo group, a finding of no difference (e.g. in an active control study) could mean that both drugs are effective, neither were effective, or that the study design was unable to tell effective from ineffective treatment (128). TONES 5 included a randomised placebo-controlled withdrawal phase to assess the reversal of solriamfetol effect upon treatment discontinuation after prolonged treatment (≥6 months). This study design was included at the request of the FDA, to provide well-controlled evidence of the long-term efficacy of solriamfetol in EDS and to evaluate any potential withdrawal effects.

Comparison of study populations to the UK narcolepsy population

TONES 2 and TONES 5 were both large, multinational, well conducted and methodologically robust Phase 3 studies conducted in North America and Europe. Although TONES 2 and TONES 5 were multinational trials, there were no clinical sites in the UK. Similarly TONES 1 was conducted solely in the United States.

In patients with narcolepsy in TONES 2, TONES 1 and TONES 5, respectively 65.3%, 64.5% and [redacted] were female, mean (SD) age was 36.2 (13.2), 38.7 (12.1) and [redacted] years, median age ranged between [redacted] years, cataplexy was present in 50.8%, 35.5% and 50.4% of patients, and mean baseline ESS was 17.2 in TONES 2, 17.3 in TONES 1 and 15.9 in TONES 5 (for Group A at parent study baseline and for Group B at TONES 5 baseline), indicating high levels of EDS in these patient populations (see Section B.2.6).

Information on the demographics of the narcolepsy population in the UK is extremely limited. The available data are based on results from three UK Narcolepsy Association surveys[q] which indicate that (45, 73, 129):

- 51.1–60.7% of patients are female
- Median age is 54–56 years
- Mean (SD) ESS scores are:
  - 19.6 (3.0) for patients with narcolepsy with cataplexy
  - 16.9 (4.8) for patients with EDS without cataplexy

The characteristics of the trial populations were broadly consistent with those of the UK survey respondents. Approximately 50–60% of the survey respondents were female, compared with approximately two-thirds of the clinical trial populations. The median age of patients in the UK surveys is higher than that observed in the clinical trials, however the survey data are outdated (date range: 1998–2004), and the trials only included adults 18–75 years, whereas the survey patients were 12–89 years old; furthermore, there is a widely recognised delay to diagnosis for patients with narcolepsy in the UK (49), and these factors may have contributed to the higher median age of the survey respondents. Only one survey reported ESS scores (129), and these were consistent with those of the trial population: both populations had mean ESS scores outside the normal range (i.e. had ESS scores >10; Table 6).

[q] Parkes 1997: 183 patients with narcolepsy, 62 patients with hypersomnia, 10 patients with OSA and 188 controls returned self-report questionnaires; Daniels 2001: 313/500 patients with narcolepsy returned questionnaires; Morrish 2004: 313/500 patients with narcolepsy returned questionnaires.

Trial populations compared with marketing authorisation and use in clinical practice

Both TONES 2, TONES 1 and TONES 5 provide evidence in patient populations relevant to the final NICE scope. The trials included patients with EDS due to narcolepsy (with or without cataplexy), consistent with the use for solriamfetol in UK clinical practice and the indication:

- "Solriamfetol is indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy)"

The proposed positioning of solriamfetol in UK clinical practice would be as a follow-on treatment subsequent to modafinil failure or intolerance, or where modafinil is contraindicated. The overall trial populations (including patients who received unlicensed 300 mg dose) are consistent with this positioning in that very few patients were treatment naïve (prior use of a stimulant/other nervous system drug: TONES 2, [redacted] TONES 5, [redacted] and almost half had prior modafinil treatment ([redacted] TONES 2; [redacted] TONES 5). The high level of previous modafinil use is consistent with the first-line status of modafinil for narcolepsy in UK clinical practice (1, 54).

Relevance of trial dosing to marketing authorisation and use in clinical practice

All trials (TONES 2, TONES 1 and TONES 5) covered the range of doses included in the licence for solriamfetol in narcolepsy (75 and 150 mg), and the use of this treatment in clinical practice in the UK. Based on guidance in the SmPC, patients in clinical practice may be titrated up from a starting dose of 75 mg to 150 mg "Depending on clinical response…". In solriamfetol clinical trials for narcolepsy titration between 75 and 150 mg doses was only applicable in TONES 5, and in this study, titration was forced to the maximum dose based on tolerability. In TONES 5, the ratio of 75 to 150 mg doses, by modal dose was approximately 1:4. Although some patients in TONES 5 may have been up titrated based on good tolerability, they may not have required the higher dose from an efficacy perspective. As such, although this study represents the only evidence based estimate of the dose split between the 75 and 150 mg doses it may not be fully reflective of the dose split that may be observed in clinical practice and is inconsistent with prescribing data from US experience to date, where the dose split is approximately 1 to 1.

Relevance of outcome measures to clinical practice

TONES 2, TONES 1 and TONES 5 included clinical outcomes relevant to the final NICE scope. The primary endpoint of ESS was measured across the trials and is a well-recognised, clinically-relevant, subjective outcome measure consistent with that used in UK practice. The ESS is used to measure levels of sleepiness and to assess the efficacy of treatment in reducing sleepiness (87, 88, 93-95).

Changes of ≥3 points in the ESS score are generally considered clinically meaningful in assessing EDS (see Table 6), although based on KOL Clinical Practice Interviews, the majority of clinicians stated that they accept differing and often lesser levels of improvement than this, and consider any patient-reported improvement to be meaningful. In TONES 2, patients receiving solriamfetol 75 mg and 150 mg achieved a ≥3 point reduction in mean ESS scores (-3.8 and -5.4 point reduction, respectively) after 12 weeks of treatment, compared with -1.6 for placebo (see Section B.2.6.1.1), and in TONES 5, patients in solriamfetol 75 and 150 mg arms achieved a ≥3 point reduction in mean ESS scores (mean reduction, respectively: Group A [redacted] and [redacted] Group B, [redacted] and [redacted]) after 2 weeks of treatment, maintained through week 40 for Group A [redacted] and [redacted], respectively), and week 52 for Group B [redacted] and [redacted], respectively; see Section B.2.6.3.2.1).

The categorisation of EDS into mild, moderate, or severe based on ESS scores is frequently used in the literature on narcolepsy but feedback from the KOL Clinical Practice Interviews suggests that it is extremely uncommonly used in UK clinical practice. This feedback further suggests that the use of ESS scores alone to assess improvements in EDS is highly variable, with many clinicians instead using a more holistic approach, assessing patient-reported improvements to determine treatment response – i.e. it is the patient's report of a reduction in the impact of narcolepsy on daily function that helps define a positive response. In situations where only ESS is used to determine response, the absolute reduction in ESS required to define response also varies widely, with some KOLs reporting that any reduction is meaningful if the patient feels improved but others using an absolute reduction of 2–4 points. Furthermore, the MWT is rarely used in UK clinical practice except as an initial diagnostic test (due to the cost and inconvenience of conducting the test). This is consistent with the results of a study that demonstrated

[redacted] were more strongly correlated with [redacted] (130). In TONES 2 and TONES 5, the clinically meaningful reductions in ESS scores were associated with significant improvements in patient-reported PGI-c scores, indicating that patients felt their EDS had improved following treatment with solriamfetol for 12 weeks and up to 52 weeks, respectively. The outcome measures used in the TONES trials are therefore relevant for clinical practice where both types of assessment (absolute reduction in ESS and subjective reports of improvement) are used to determine treatment response.

QoL impact measured using validated, disease specific and generic specific tools

The impact of treatment on QoL was assessed using validated, generic and disease-specific tools: EQ-5D-5L, SF-36v2, FOSQ-10. The EQ-5D-5L is a standardised measure of health utility that provides a single index value for one's health status (100), and would ordinarily be seen to be of most relevance to modelling the economic impact of solriamfetol, in line with the NICE reference case. The SF-36v2 is a generic measure of health status with 36 questions across 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) (99).

In contrast, the FOSQ-10 is a 10-item, disease-specific, QoL questionnaire developed to measure the effect of disorders of EDS on functional status and activities of daily living, and/or the extent to which these effects are improved with treatment for EDS (98, 131). The FOSQ captures the impact of sleepiness on functional status across 5 subscales (activity level, general productivity, social outcome, intimacy and sexual relationships, and vigilance) and as a total score (range 5–20), where higher scores indicate greater functional status (98).

Variation in boundary of normal ESS range

In the UK, ESS scores ≤10 are considered 'normal' daytime sleepiness (Table 6), thus in clinical practice, patients with narcolepsy would usually have ESS scores substantially in excess of 10 at treatment initiation. The eligibility criteria for

TONES 2 included patients with ESS scores ≥10, thus a small proportion of patients in the trial had normal ESS values (ESS=10) at baseline: solriamfetol 75 mg, [redacted]solriamfetol 150 mg,[redacted] For the purposes of cost-effectiveness analyses, as presented in Section B.3, analyses were conducted using individual patient level data (IPD), and patients with baseline ESS=10 were excluded from the effectiveness estimates utilised for solriamfetol.

Availability of comparative evidence

The ITC analysis included seven trials, all of which were RCTs, ensuring that effects were observed under similar conditions, with similar baseline levels of sleepiness and wakefulness, measured using ESS and MWT, amongst the seven trials.

All studies were placebo-controlled enabling the generation of networks that were linked through a common placebo node. However, there were no head-to-head trials to allow testing of assumptions of consistency (i.e., comparisons of direct and indirect evidence). In addition, there were only two or three trials per comparator and not every trial reported every outcome, which limited the strength of the networks and the ability to test for heterogeneity in outcomes.

Efficacy estimates could be generated for a range of outcomes which were specific for both drug dose and duration on therapy, other than for pitolisant where estimates were not available from studies stratified by dose. In relation to time on therapy, some assumptions had to be made to make comparisons feasible, e.g. outcomes measured at 7 weeks were assumed to fit to the 8 week timepoint. In addition, the TONES 1 and TONES 2 trials were of 12 weeks' duration, with primary endpoints assessed at week 12, whereas trials for pitolisant and sodium oxybate lasted no more than 9 weeks. Therefore, it was not possible to assess comparative treatment effects for the trial outcomes at the 12-week timepoint (details of the analyses conducted are presented in Section B.2.9.1). With regard to dosing, two of the sodium oxybate trials used non-recommended approaches to administration. The SmPC states that sodium oxybate (Xyrem) is initiated at 4.5 g and titrated over 1-2 weeks in 1.5 g doses to higher levels (66). However, in Xyrem, 2002, patients were randomised to either 3 g (stable dose but lower than the recommended dose), 6 g, or 9 g without any titration (109); in Black, 2006, patients randomised to sodium

oxybate were initiated on 6 g sodium oxybate (115). Efficacy outcomes for the 3 g dose should therefore be disregarded, while safety outcomes for non-titrated doses should be considered carefully in light of this divergence from SmPC recommendations. Finally, in relation to outcomes, some efficacy outcomes that were reported in the TONES 2 trial for solriamfetol (i.e., FOSQ, EQ-5D) were not reported in comparator trials and therefore could not be analysed.

With regard to comparators, a weakness in the analysis is the limited evidence available for dexamfetamine and methylphenidate; the SLR did not identify any first-level evidence (RCTs) for dexamfetamine or methylphenidate, and although limited observational data for these comparators was identified, the data was insufficient to be included in the ITC. This restricted the potential analysis at best to a naïve comparison between solriamfetol and dexamfetamine or methylphenidate. However as this would be subject to substantial bias and it would not be possible to control for differences in the patient population and baseline characteristics, a naïve comparison was not conducted.

B.2.13.3 End of life

Solriamfetol is not a life extending treatment and does not qualify for any end of life criteria.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify published economic evaluations for patients with narcolepsy. The SLR identified six records in total: three published economic evaluations and three health technology assessment (HTA) submissions. Full details of the SLR are presented in Appendix G, including a summary of the studies identified.

Of the three published economic evaluations identified (two full text publications (132, 133); one conference abstract (134)) which reported the cost-effectiveness of treatments for narcolepsy, one was conducted from a UK perspective (133), and the remainder were from a European perspective (132, 134).

All three previous HTA submissions assessed sodium oxybate for the treatment of patients with narcolepsy and cataplexy, two within Scotland (to the Scottish Medicine Consortium [SMC]) and one for Canada (to the Canadian Agency for Drugs and Technologies in Health [CADTH]) (135-137). Details of the approaches to modelling adopted in the previous HTA submissions were limited. None of the submission summary documents available to the public provided any information regarding the model structure, perspective, discounting, or time horizon.

The SLR did not identify any NICE technology appraisals for treatments in narcolepsy. An ad-hoc search of the NICE website was therefore performed (on 8th August 2019; not part of the SLR methodology) to identify any technology appraisals conducted in OSA, as this patient population also experiences EDS. This identified one additional HTA NICE TA139 “Continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnoea/hypopnoea syndrome (OSAHS)”, hereafter referred to as TA139 (138), which is summarised in Table 37. Although the focus of TA139 is predominantly on treating the underlying cause of the OSAHS, EDS is a commonly reported symptom in patients with OSA and therefore this population has some parallels with patients with EDS due to narcolepsy, as assessed in the present technology assessment.

The two UK-specific cost-effectiveness analyses (Lanting 2014 (133) and TA139 (138)) have been used to inform various aspects of the current modelling methods, inputs and assumptions, and these are described in the relevant subsections throughout Section B.2.3.

To summarise, the analyses presented here are:

- Two models associated with TA139:
  - The model developed by ResMed for the TA139 submission
  - The model developed by the Assessment Group for TA139 and subsequently published as a report, hereafter “McDaid 2007” (139)
- The analysis published by Lanting 2014 (133)

Table 37. Relevant NICE submissions (in OSA only; not identified through SLR)

Study, country, design	Population	Intervention and comparators	Model summary	Study perspective	Discounting	Time horizon	Model inputs (clinical, costs, QoL)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE 2008 (138, 139) [*full submission]* UK CUA – Manufacturers submission (ResMed)	Adults with severe OSAHS and daytime sleepiness (55 years old)	• CPAP • No treatment	Markov model: • Event free • CV event • Stroke • RTA • Death	• UK NHS • PSS	NR	14 years	• Clinical: NR • Costs/ Utilities: List prices, published literature, government statistics, authors' assumptions	NR	NR	• CPAP (fixed): -£1,620 (-£4,123 to £259) • CPAP (auto): -£1,845 (-£3,936 to £37)
NICE 2008 (138, 139) [*full submission]* UK CUA – York	Adults with severe OSAHS and daytime sleepiness (Male, 50 years old)	• CM • CPAP • Dental devices	Markov model: • Event free • CV event • Stroke • RTA	• UK NHS • PSS	3.5% on both costs and health effects	Lifetime	• Clinical: NR • Costs/ Utilities: List prices, published literature, government statistics, authors' assumptions	• CM: £8,140 • Dental devices: £8,797 • CPAP: £9,301	• CM: 11.93 • Dental devices: 12.26 • CPAP: 12.39	• Dental devices: £2,000 • CPAP: £4,335

Abbreviations: CM, conservative management; CPAP, continuous positive airway pressure; CUA, cost-utility analysis; CV, cardiovascular; ICER, incremental cost-effectiveness ratio ; NHS, National Health Service; NICE, National Institute of health and Care Excellence; NR, not reported; OSA, obstructive sleep apnoea; OSAHS, obstructive sleep apnoea hypopnoea syndrome; PSS, personal social services; QoL, quality of life; RTA, road traffic accident; SLR, systematic literature review; QoL, quality of life; QALYs, quality-adjusted life years.

B.3.2 Economic analysis

The objective of the economic evaluation for this submission was to assess the cost-effectiveness of solriamfetol for the treatment of EDS in patients with narcolepsy, versus all relevant comparators as defined in the company decision problem (Table 1).

A two-stage model was developed in Microsoft® Excel 2016, to model the outcomes and costs experienced by a patient cohort comprising adult patients who suffer from EDS due to narcolepsy, over a lifetime time horizon; a decision tree reflected the first 8-weeks of treatment and a Markov model, with annual cycles, was used for the remainder of the model time horizon. The model reported health outcomes including life years (LYs), QALYs and direct costs. The model perspective was the NHS and Personal Social Services (PSS) in England.

The model improved upon the approaches used in models identified in the SLR for narcolepsy (see Section B.3.1) and in TA139 (138), by utilising IPD from the TONES 2 clinical trial to define responders and non-responders to treatment, combining output from the ITC (see Section B.2.9.2.2) to allow a robust comparative analysis, and demonstrating the associated treatment-related changes in ESS.

The OSA models (from TA139) had a single EDS health state linked to the specific treatment being administered, which was modelled as a mean change in ESS from baseline and an associated impact on QoL. This mean change in ESS was attributed to the entire cohort and it was assumed that all patients accrued associated treatment costs for the duration of the model. The use of a single treatment associated health state assumed that all patients achieved the same level of response, i.e. the mean change in ESS, however this represents a limitation of this approach. Feedback from the KOL Clinical Practice Interviews suggests that in practice although some patients do respond to the existing treatment options, there is a proportion of patients who do not respond *or* have an initial response that wanes over time, and these patients typically switch (or discontinue) treatment.

Given this information from the KOLs, the assumption (that all patients achieve a mean ESS reduction) made in the OSA models for TA139 would therefore have

included some patients that, in clinical practice, would be classified as non-responders and would be switched to another treatment or discontinue treatment. As such the model analyses may have overestimated the associated treatment costs and potentially underestimated the potential treatment efficacy. Whilst this is less important in the OSA population considered within TA139, where patients need to remain on a primary OSA therapy, such as CPAP, in order to treat the underlying cause of their condition, it is perhaps more important for a wake-promoting agent where the purpose of treatment is specifically to reduce a patient's level of EDS. The analysis described herein aimed to address the above limitation by identifying responders and non-responders, and by continuing or discontinuing treatment accordingly.

The UK analysis by Lanting 2014 (133) identified in the clinical SLR was specific to narcolepsy, and was a two-part model that utilised a decision tree for the initial three months of treatment, and split patients into responders, non-responders, or discontinuers due to AEs. Patients then entered a three state Markov model for the remainder of the analysis (five-years), for which the health states were: (1) on treatment with maintained response, (2) withdrawn from treatment, no response and (3) dead. Whilst this approach addressed some of the model structure limitations of the TA139 model (by identifying responders and non-responders to treatment), there were still weaknesses with the data; for example, the rate of responders was informed by clinician opinion.

The current model, developed for this technology assessment, built on the approach used by Lanting 2014 (133), as it utilised IPD from patients with EDS due to narcolepsy who were enrolled in the pivotal RCT for solriamfetol in narcolepsy (TONES 2) to estimate the treatment effect for solriamfetol on EDS, as measured using ESS. Comparative effectiveness was based on the outputs of the ITC, as reported in Section B.2.9. Although no formal treatment pathway exists in the UK for patients with EDS due to narcolepsy, the model attempted to reflect the current management of patients described by the KOL Clinical Practice Interviews (which suggest that subjective reports of improvement in symptoms (such as the ESS) are deemed an important clinical outcomes in managing EDS due to narcolepsy), and

therefore the model focused on a reduction in ESS scores as the measure of response.

Categorisation of patients into EDS severity bandings – no EDS (ESS: 0-10), mild EDS (ESS: 11-14), moderate EDS (ESS: 15-18), severe EDS (ESS: 18-24) – as outlined by NICE Clinical Knowledge Summary (140), was considered for health states in the current model, but this approach was deemed to be inappropriate for several reasons:

- Feedback from the KOL Clinical Practice Interviews suggests that in the UK clinicians rarely categorise patients into mild, moderate or severe EDS, and do not use transitions across categories to assess response to treatment (2), therefore as these definitions (mild, moderate, severe) are not routinely used in clinical practice, they were not included within this submission.
- Furthermore, although a reduction in ESS of 2–4 is reported to be a clinically relevant change (90, 91), respondents to the KOL Clinical Practice Interviews advised that achieving a pre-specific absolute change in ESS is not the only determinate for assessing treatment response, and that instead any reduction in ESS may be considered meaningful if the patient self-reports a positive impact of treatment on their EDS or daily function.
- In light of the KOL feedback, it would have been inappropriate to categorise health states using ESS scores within the model, due to the following limitations of this approach:
  - In defining EDS categories using ESS scores, some patients could achieve an ESS response (i.e. ≥3 points reduction in ESS) but may not change health state; for example, a patient that improves from ESS=18 to ESS=15 is a ‘responder’ to treatment but remains within the moderate EDS category.
  - Conversely, patients with baseline ESS scores close to the boundaries between EDS categories may switch health states, in a modelling context, but achieve an ESS improvement that is smaller than the clinical response criteria; for example, a patient that improves by 1 point from ESS=15 to ESS=14 is considered a ‘non-responder’ to treatment but has switched from a moderate EDS to a mild EDS category; this may inaccurately imply that a

patient who achieved a change of health state had a greater improvement than a patient who achieved a 3 point reduction in ESS.

- In a modelling context, if EDS categorisation had been used to define health states within the current model, this would have resulted in scenarios where patients were receiving and responding to treatment, but were not changing health state (and therefore not achieving any clinical benefit), as defined by a health state-related utility, and this patient scenario would therefore underestimate the actual benefit of treatment in the current model.

This analysis therefore focused on identifying patients that had responded or not responded to therapy, by looking at the absolute change in ESS from baseline, irrespective of the baseline ESS score. This was expected to be more reflective of UK clinical practice. For the purposes of the analysis response was defined as a ≥3-point reduction in ESS from baseline, the mid-point of the range cited in the literature (90, 91); with scores of 2 and 4 tested in scenario analysis.

Although not directly relevant to the current decision problem (to assess solriamfetol for treating EDS caused by narcolepsy), TA139 assessed CPAP treatment for OSA (a condition in which patients also experience EDS) and therefore TA139 offered some additional considerations for the current analysis. As part of the multiple technology appraisal process for TA139, the assessment group developed a state-transition Markov model to assess the long-term cost-effectiveness of CPAP compared to other OSAHS treatments. The assessment group's model had a lifetime horizon and accounted for the symptomatic effects of OSAHS on QoL using a treatment-related change in ESS. Within the analysis, patients entered the model with a mean treatment-adjusted ESS score which persisted for the entire time horizon unless patients experienced an event. Our analysis attempted to improve upon this by categorising patients as responders and non-responders, therefore avoiding the unnecessary use (and associated costs) of pharmacological therapy in patients who did not benefit from their treatment.

The models in TA139 incorporated the involvement in road traffic accidents (RTAs). There is an association between EDS and increased risk of RTAs (141), however in the UK, narcolepsy (142) is considered a 'notifiable' medical condition by the DVLA,

and patients with uncontrolled EDS must surrender their driving licence; these patients must then meet the medical standards for driving before returning to driving, however it is unclear what the standards for restarting driving entail (143). Within the general population the risk of being involved in an RTA is very small: the Department for Transport Reported road casualties in Great Britain: 2018 Annual Report (144), states '*the rate of fatalities per billion vehicle miles has fallen by 1% from 5.43% in 2017 to 5.38% in 2018*'. The average car travels approximately 7,600 miles per annum (145) and the risk of a car being in a fatal RTA is about $4.1x10^{-8}$. Similarly, the report states '*The casualty rate per billion vehicle miles travelled has decreased throughout 2008 to 2018 from 735.7 to 484.5 casualties per billion vehicle miles*' equating to a $3.7x10^{-6}$ risk of a car being involved in an RTA resulting in a casualty. Consequently, despite the evidence for an increased risk of RTA in patients with EDS, based on the small risk of an individual in the general population being involved in an RTA, combined with the stipulation that patients considered in the analysis (i.e. patients with EDS due to narcolepsy) should not be driving due to their notifiable medical condition, it was assumed that modelling RTAs was inappropriate and this was excluded from the current analysis.

The models for TA139 also incorporated the possibility of cardiovascular events or strokes. This was achieved by modelling changes in systolic BP, associated with the respective treatments, using the Framingham risk equations (138, 139). The NICE Committee for TA139 noted that excluding the effect of CPAP on cardiovascular events in the model did not lead to significant changes in the incremental cost-effectiveness ratio (ICER). This is unsurprising given the very small treatment related changes in systolic BP and the lack of conclusive evidence on the effect of BP and cardiovascular events. As noted in Section B.2.10.3.3, the impact of solriamfetol on systolic BP is minimal/negligible, therefore it was assumed that modelling cardiovascular events and stroke was inappropriate and this was excluded from the current analysis.

B.3.2.1 Patient population

The current model included adult patients with EDS due to narcolepsy (diagnosed according to the ICSD-3 as per the TONES 2 eligibility criteria; Table 4), where EDS was defined as a baseline ESS score >10 (87). This is broadly consistent with the

populations defined in the NICE scope (see Table 1), the TONES trials (see Section B.2.6.1and B.2.6.3), and the European marketing authorisation of solriamfetol (see Appendix C).

The TONES studies included patients with ESS scores ≥10, thus a small proportion of patients in the trials had normal ESS values (ESS=10) at baseline (solriamfetol 75 mg, [redacted] solriamfetol 150 mg, [redacted]). For the purposes of the cost-effectiveness evaluation, the EDS definition of ESS >10 was assumed and as such, all patients with a baseline ESS=10 were excluded from the IPD for TONES 2 that was utilised in the model.

The demographics and baseline disease characteristics of the model cohort were based on the solriamfetol 150mg mITT population of TONES 2, defined as all randomised patients who received at least one dose of study drug, and had a baseline and at least one post-baseline evaluation of ESS. The mITT population was used for the model cohort as this was consistent with the population used to analyse the primary efficacy endpoint in the trial (see Table 12). All patients with a baseline ESS=10 were excluded. The analysis was limited to the solriamfetol 150 mg dose data due to the methodology used to synthesise the relative treatment effect for the comparators in the ITC (see Section B.2.9). Although this is a limitation of the analysis, the baseline characteristics for the solriamfetol 150 mg group were consistent with the overall trial population (Safety Population; see Section B.2.3.2).

Key baseline characteristics of the model cohort were taken from the TONES 2 trial cohort and are described in Table 38. Information on the demographics of the narcolepsy population in the UK is extremely limited and restricts the ability to make comparisons between the trial population and the population of patients with narcolepsy in England. The available data are based on results from three UK Narcolepsy Association surveys[r] which indicate that (45, 73, 129) (see Section B.2.13):

[r] Parkes 1997: 183 patients with narcolepsy, 62 patients with hypersomnia, 10 patients with OSA and 188 controls returned self-report questionnaires; Daniels 2001: 313/500 patients with narcolepsy returned questionnaires; Morrish 2004: 313/500 patients with narcolepsy returned questionnaires.

- 51.1–60.7% of patients are female, which is broadly consistent with TONES 2 in which ~65% of the population were female.
- Median age of patients with narcolepsy in the UK is reported as 54–56 years, however as the UK Narcolepsy Association survey data are outdated (date range: 1998–2004) this age range may no longer be representative of the UK population of patients with narcolepsy; furthermore, as the survey respondents were between 12 and 89 years old, but the trials were restricted to adults 18–75 years, the difference in the age ranges included may explain the differences between the surveyed population and TONES 2 (49).

Table 38. Patient population included in the economic model

Baseline characteristics	Overall TONES 2 population (Safety population)	Overall TONES 2 population (mITT†)	Value used in model (mITT solriamfetol 150 mg arm†)	Source
Age, years	[redacted]	[redacted]	[redacted]	TONES 2
Female, %	[redacted]	[redacted]	[redacted]	
ESS score at baseline	[redacted]	[redacted]	[redacted]	

Abbreviations: ESS, Epworth Sleepiness Scale; mITT, modified intent to treat; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Data are presented as mean (SD) unless otherwise stated
† Based on [redacted], excluding patients with an ESS=10 at TONES 2 baseline.

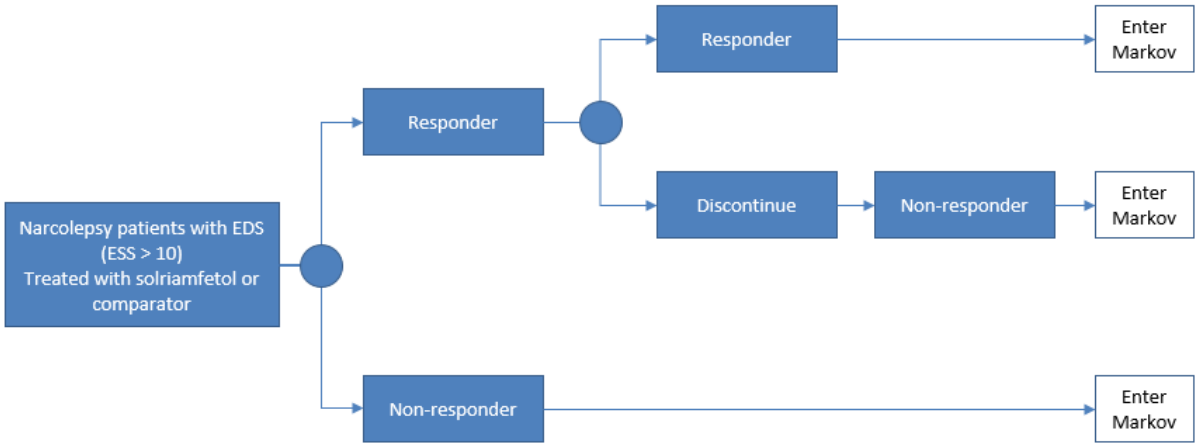
The model considered patients who have failed or are intolerant/contraindicated to modafinil, reflecting the proposed positioning of solriamfetol in UK clinical practice (see Section B.1.1). This positioning is based on the Sleep Services Analysis and KOL Clinical Practice Interviews which indicate that modafinil is an established first-line treatment for narcolepsy in the UK and that solriamfetol would be considered as an option for patients in whom modafinil has failed, has not been tolerated or is contraindicated (1, 2). A scenario analysis assessed the cost-effectiveness of solriamfetol in the subset of the TONES 2 IPD, in which patients had previously been treated with modafinil.

B.3.2.2 Model structure

The analysis used a two-stage model developed in Microsoft® Excel 2016 consisting of a decision tree (Figure 14), that determined responder and non-responder status at 8 weeks, followed by a Markov model with annual cycles (Figure 15) that

estimated outcomes for each treatment over the remainder of the model lifetime time horizon. Responder and non-responder patients, as determined by the decision tree model, were then moved to the corresponding health state in the Markov model, for each treatment arm: the Markov model was applied from week 8 onwards, and contained three health states: responder, non-responder, or death.

Figure 14. Treatment initiation – Decision tree schematic



Abbreviations: EDS, excessive sleep disorder; ESS, Epworth Sleepiness Scale.
A responder is defined as a patient achieving a reduction in ESS ≥3.

All patients entered the initial decision tree model with the same baseline ESS score and received treatment with either solriamfetol, dexamfetamine, methylphenidate, sodium oxybate or pitolisant. Patients were then either classified as “responders”, defined as patients who have achieved a ≥3-point reduction in ESS after 8-weeks from baseline (see Section B.3.3.1), or “non-responders”.

Based on the timing of the first post-baseline ESS measurement within TONES 2, the treatment effect of solriamfetol on ESS was observed within 1 week of treatment initiation (see Section B.2.6.1.2). However, the comparator trials reported a first post-baseline measurement at time points of 2, 4 or 7 weeks (107) which did not allow a fair comparison between treatments in terms of how early the treatment effect may be observed. For simplicity, the improvement in ESS and the associated impact on QoL were assumed to occur after 1 week of treatment initiation for all treatments, based on evidence from TONES 2 and 5, although this may have overstated the efficacy for some comparators.

Although the improvement in ESS occurred from the first week, the decision to continue treatment (i.e. to define a patient as a 'responder' in the model) was based on a clinical assessment of response conducted at week 8. Response to treatment (≥3 point reduction in ESS from baseline) was assumed to be assessed at 8 weeks post-initiation in order to reflect the availability of data from comparator trials (see Section B.2.9). Although there were available data for solriamfetol at 12 weeks post-treatment initiation (i.e. the primary endpoint,) the available comparator data for use in the ITC were limited to a maximum of 8 weeks. The KOL Clinical Practice Interviews suggests that the time between routine follow-up assessments/visits can vary significantly in practice, ranging from 6 weeks up to 6 months, sometimes influenced by limited capacity within the service (2). In the absence of an established time point for clinical assessment, and based on the availability of the most robust comparative clinical evidence at week 8, patients were assumed to accrue the drug cost associated with each treatment for a minimum of 8 weeks (at which stage treatment response was assessed), and the 12-week timepoint was considered in a scenario analysis (see Section B.3.8.4).

Although patients were categorised as responders and non-responders it should be noted that the relative level of response, as measured by change in ESS, varied for each of the comparator treatments. As such, the proportion of patients achieving response (≥3 point reduction in ESS from baseline) and the mean absolute change in ESS from baseline for responders and non-responders, across all treatments considered, was recorded and used to estimate the associated impact on QoL.

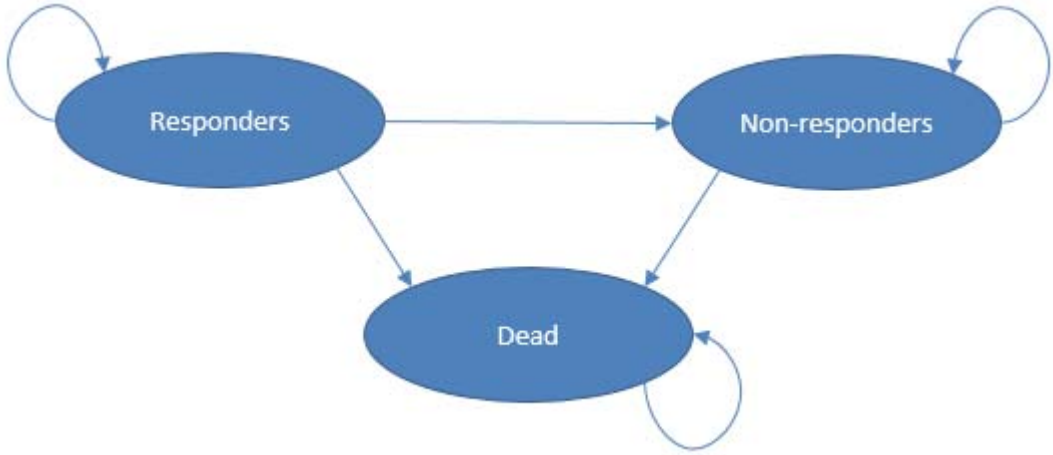
Following the 8-week decision tree phase, patients moved into a Markov element for the remainder of the model time horizon, with annual cycles. Annual cycles were chosen because narcolepsy is a chronic condition for which there is no cure, and in the absence of evidence to support any movement between the health states at a more granular cycle length. Half cycle correction was incorporated to address the long-cycle length, and in line with the NICE reference case. The model consisted of three mutually exclusive health states:

- Responders: on treatment with a maintained response (defined as the treatment-specific change in ESS).

- Non-responders: those patients who have not achieved a response or have withdrawn from treatment due to AEs or subsequent loss of efficacy (returning to the mean baseline ESS).
- Dead: absorbing health state.

Those patients who entered the response state were assumed to have a reduced ESS score, specific to the treatment received, and the associated treatment cost whilst they remained on therapy. Long-term solriamfetol data from TONES 5 demonstrated that in the first year following initiation, the ESS improvement remained relatively constant in responders. As previously noted, both the Lanting 2014 and TA139 assessments assumed a constant effect of treatment over the respective model time horizons; based on these prior analyses and in the absence of any data available for solriamfetol or the comparators to quantify any waning effect, it was assumed that patients that responded to any treatment remained in that response state, using the same treatment-adjusted ESS for the duration of the analysis, unless they discontinued therapy.

Figure 15. Maintenance treatment – Markov Model schematic



Evidence from the Sleep Service Analysis and KOL Clinical Practice interviews (1, 2) suggests that “non-responders” will cycle through a number of pharmaceutical-based treatments for EDS during their lifetime (2). As described in Section B.1.3, modafinil is a widely established first-line treatment in UK clinical practice for managing EDS due to narcolepsy. In patients who have failed, are contraindicated to, or are intolerant to modafinil, there is no established second-line (or subsequent-line)

therapy, and although local guidelines and treatment algorithms exist, there is substantial variability in practice, depending on clinical opinion, preference, and local funding and/or guidelines. There are therefore no robust data available to predict the treatment sequence that may be employed, nor is there any clinical evidence to demonstrate the relative efficacy of the therapies at subsequent lines of treatment. Given the lack of appropriate data, and for simplicity, this analysis assumed that all non-responders remained in the same state and therefore the model excluded subsequent treatment sequences; excluding the costs and potential impact of subsequent treatments was a conservative and simplified assumption for solriamfetol 150 mg, which has equivalent or greater efficacy compared to all comparators considered in the ITC (pitolisant, sodium oxybate).

This approach was consistent with Lanting 2014 (133) which assumed that those who did not respond or who discontinued entered a 'withdrew from treatment' state and remained there until death. Both analyses within TA139 simply assumed patients remained in an OSA state (which was associated with an ESS related utility score), thereby implying that there is no change in treatment for EDS over the time horizon.

The current model used the IPD from TONES 2 to determine the proportion of patients who were responders and non-responders, and the associated mean change in ESS from baseline in each responder/non-responder group for solriamfetol 150 mg. For the comparators, a pseudo-IPD dataset was synthesised utilising the mean change in ESS from baseline relative to solriamfetol (see Section B.3.3.1 and B.3.3.2).

B.3.2.3 Time horizon

Narcolepsy is a chronic condition with no cure (11, 12). As a consequence, this analysis assumed a lifetime horizon, in line with current NICE guidance (146). The model assumes an average starting age of 38 years and lifetime is defined in the model base case analysis of 70 years. Alternative time horizons were considered in sensitivity analyses.

B.3.2.4 Mortality

The model utilised sex- and age-specific all-cause mortality data from the Office of National Statistics life tables (147) to estimate annual mortality rates. The model assumed no treatment-related impact on mortality but Ohayon 2014 (148) reported a 1.43 fold excess mortality in females and 1.57 fold in males with narcolepsy relative to those without narcolepsy and this was incorporated into the analysis for completeness.

B.3.2.5 Perspective and discounting

The base case analysis took the perspective of the NHS and PSS in England. Both cost and outcomes (LYs and QALYs) were discounted at 3.5%, in line with the NICE Guide to the Methods of Technology Appraisal 2013 (146). The impact of discounting at 0% and 6% was assessed in sensitivity analyses.

B.3.2.6 Model outcomes

Model outputs included total costs and QALYs for each treatment as well as the incremental values, allowing calculation of the ICER, expressed as cost per QALY gained. Only direct costs were included, with indirect costs included as a scenario analysis. LYs for each treatment were reported but due to no assumption of a treatment-related impact on mortality the number of LYs estimated remained the same for each treatment.

B.3.2.7 Features of the economic analysis compared with previous appraisals

As described in Section B.3.1, the economic SLR did not identify any previous NICE TAs for treatments for EDS in patient populations with narcolepsy.

However, hand-searching of the NICE website identified TA139 (138) which considered CPAP for the treatment of OSAHS; although CPAP is used to treat the underlying condition in OSA, EDS is a residual symptom of OSA that may occur even in patients who are CPAP-treated, thus it was reasonable to assume that TA139 could provide useful insights for modelling treatments for EDS in a narcolepsy population. A summary of the main characteristics and assumptions used in the

model in TA139 and the comparison with the current economic evaluation is provided in Table 39.

Table 39. Features of the current economic analysis

	Previous appraisals	Current appraisal	
Factor	**TA139 (CPAP for OSA) Assessment group model**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	In line with the NICE Reference Case
Treatment waning effect?	Not considered	Treatment discontinuation due to lack of efficacy is incorporated using data from TONES 5	TONES 5 presents data directly relevant to the decision problem and no evidence to the contrary
Source of clinical data	Pre- and post-treatment ESS scores from identified RCT data (149-152)	TONES 2	TONES 2 is the pivotal RCT for solriamfetol in treating EDS due to narcolepsy as defined in the NICE scope. An ITC (Section B.2.9.2) presents the best available comparative evidence in the absence of head-to-head RCTs.
Source of utilities	ResMed company submission: A before and after study (150) Assessment Group analysis: IPD from a clinical study mapping ESS to EQ-5D (153)	NHWS analysis mapping ESS to EQ-5D	In the absence of suitable trial-based EQ-5D utilities from TONES 2, and consistent with the ESS to EQ-5D mapping algorithm developed by the Assessment group, a similar approach was taken. The NHWS was considered to be the most appropriate dataset versus that used by the Assessment Group
Source of costs	ResMed company submission: Clinical expert opinion for resource use and NHS reference costs for costs Assessment Group: Aligned with the ResMed company submission	Drug Tariff (154) PSSRU 2018 (155)	Standard cost sources were used in line with the NICE Reference Case

Abbreviations: CPAP, continuous positive airway pressure; ERG, evidence review group; IPD, individual patient level data; NA, not applicable; NHS, National Health Service; NHWS, National Health and Wellness Survey; NICE, National Institute for health and Care Excellence; OSA, obstructive sleep apnoea; PSSRU, Personal Social Services Research Unit; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

B.3.2.8 Intervention technology and comparators

The intervention in the analysis was solriamfetol. The doses used were those assessed in TONES 2 and TONES 5, and per the European marketing authorisation (75 and 150 mg; Appendix C). The 300 mg dose of solriamfetol is unlicensed and therefore was excluded.

The comparators for the narcolepsy analysis were as per the company decision problem (Table 1) and are listed below:

- Pitolisant
- Sodium oxybate
- Dexamfetamine
- Methylphenidate (unlicensed for narcolepsy; see Section B.1.3)

Although modafinil was included in the NICE scope for narcolepsy this was not considered to be a relevant comparator, as evidence from the KOL Clinical Practice Interviews confirms that modafinil is the established first-line therapy for managing EDS in patients with narcolepsy and therefore solriamfetol would be considered as an option for patients in whom modafinil has failed, has not been tolerated or is contraindicated (1, 2). Therefore modafinil was not included in the company decision problem (see Section B.1.1); doses of the other comparator products are consistent with the product licences, or EFNS recommendations (11) in the case of methylphenidate (Table 40).

The amphetamines, such as methylphenidate (unlicensed in narcolepsy) and dexamfetamine, have been used for the treatment of narcolepsy since the 1930s (11) and as such, both methylphenidate and dexamfetamine are potential comparators for solriamfetol. As noted in Section B.2.9, despite a comprehensive search strategy to identify RCTs appropriate for inclusion in an ITC no evidence to inform a comparison with dexamfetamine or methylphenidate was identified. To provide additional evidence (even if of a lower quality) to inform a potential analysis, an additional comprehensive literature search of observational studies was performed to make every attempt to try to identify any data which might allow for a comparison. Despite lowering the quality threshold of the evidence base in the literature search, the only evidence that was found was for studies with very small

numbers of patients, retrospective in nature, or that were not placebo controlled (see Appendix B).

This paucity of evidence was reflected by NICE ES8 (3) which stated that “Many of these medicines are not licensed for the treatment of narcolepsy and they vary in their evidence available for their effectiveness in treating narcolepsy”. Additionally, the EFNS guidelines on the management of narcolepsy (2011) (11) mirrored the above results, identifying only 5 studies (class II and class IV evidence).

Given the paucity of robust clinical evidence for dexamfetamine and methylphenidate both were excluded from the base case analysis and were instead considered in scenario analysis. According to KOL Clinical Practice Interviews, clinicians advised that they predominantly use the MR formulations of methylphenidate (2). This is partly based on the pharmacokinetic advantages of MR methylphenidate formulations, which have a partial rapid onset, as per immediate release, but also an extended effect, due to the modified formulation component of the product. It is also partly due to clinical experience - the predominant experience of methylphenidate in the UK is amongst the paediatric population for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), where MR formulations are preferred. The British National Formulary (BNF) advises that such MR formulations should be prescribed by brand name, due to differences in the exact formulation balance of rapid- and prolonged-acting methylphenidate components. As a consequence, any analysis of methylphenidate only considered the MR formulations.

Therefore, the base case comparators were:

- Pitolisant
- Sodium oxybate

And the following were considered in scenario analyses only:

- Dexamfetamine
- Methylphenidate MR (unlicensed for narcolepsy; see Section B.1.3)

Table 40. Characteristics of treatment regimens for comparators included in the model

Drug(s)	Daily dose	Source
Solriamfetol	75 mg qd, oral	Solriamfetol SmPC (Appendix C)
	150 mg qd, oral	
Pitolisant	9.0 mg qd, oral	Pitolisant SmPC (67)
	18.0 mg qd, oral	
	36.0 mg qd, oral	
Sodium oxybate	4.5 g qd, oral	Sodium oxybate SmPC (66)
	6.0 g qd, oral	
	9.0 g qd, oral	
Dexamfetamine	10 mg to 60 mg qd, oral	Dexamfetamine SmPC (63, 64)
Methylphenidate MR (unlicensed in narcolepsy)	10 mg to 60 mg qd, oral	NICE ES8 (3) Guys and St Thomas (62)

Abbreviations: MR, modified release; qd, once daily; SmPC, summary of product characteristics.

The analysis assumed that following initiation of therapy, patients will be assessed for response by a specialist at 8 weeks. This is reflective of the available comparator clinical data which had a maximum duration of 8 weeks. The KOL Clinical Practice Interviews showed wide variability with regards to the time at which follow-up visits may occur - ranging from 6 weeks to 6 months; in some cases, this is due to limited capacity rather than clinical preference. However, because solriamfetol demonstrated equivalence or greater efficacy to pitolisant or sodium oxybate through the ITC (see Section B.2.9.2), extending the time to assessing response would mean that patients receiving comparator treatments would inappropriately remain on therapy for longer and accrue the associated drug costs; thus by considering an 8-week time point this reduced unnecessary spending beyond the 8 week assessment and was therefore a conservative assumption for solriamfetol compared with an extended time to assessment on efficacy. An alternative 12-week time point was considered in a scenario analysis, to reflect the primary endpoint of TONES 2; in this scenario the 12 week IPD was used and all patients remained on treatment up to the 12-week timepoint. Non-responders, at 8-weeks in the base case, (see Section B.3.3.1) were assumed to discontinue therapy.

B.3.3 Clinical parameters and variables

The sections below present the sources of data that informed the rate of response and the relative impact on ESS for each treatment. ESS was used as the main measure of EDS, as ESS was a co-primary endpoint in TONES 2 and TONES 5 (see Section B.2.3), and was the most commonly reported efficacy outcome across comparator RCTs identified by the clinical SLR and used in the ITC (see Section B.2.9). In addition, ESS was the primary measure of EDS used in previous narcolepsy economic evaluations (133) and when considering EDS in OSAHS (138).

MWT was considered as an alternative endpoint but feedback from the KOL Clinical Practice Interviews suggests that it is not widely used beyond initial diagnosis, (largely due to the cost and inconvenience of conducting the test, but also due to clinical preference in how treatment response is assessed) and so1616 this was not included for further analysis.

B.3.3.1 Clinical data: Response

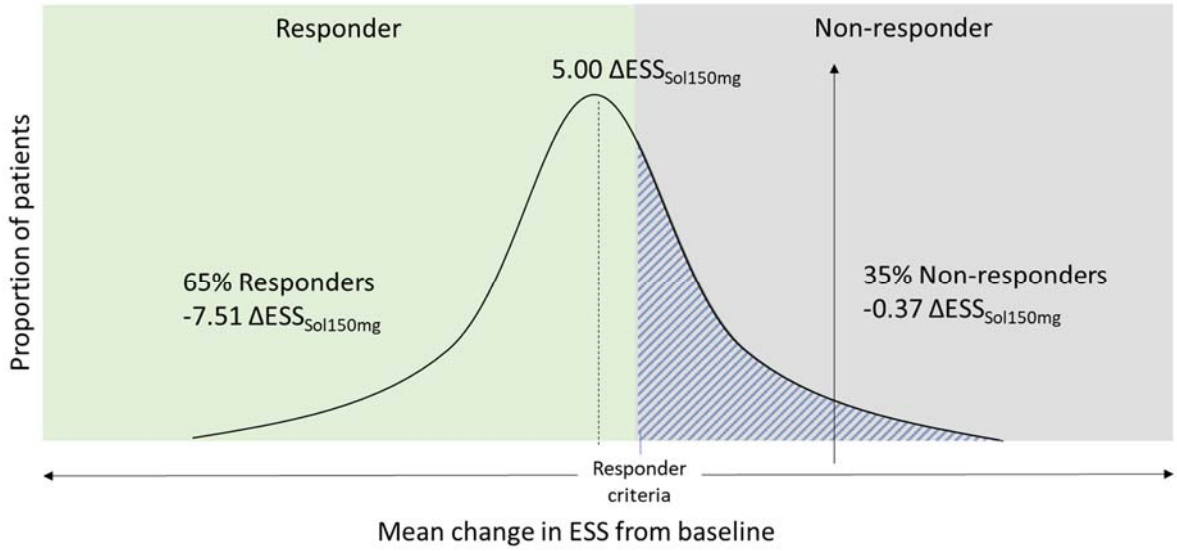
For solriamfetol

Efficacy estimates (response) for solriamfetol were determined directly from the mITT IPD from the TONES 2 trial. The IPD provided the ESS score for each patient at baseline and at week 8 which allowed for the change in ESS to be determined. The response rule was applied to these IPD to determine the proportion of responders at week 8: as described in Section B.3.2 the response rule for the base case analysis assumed that response was a reduction of ≥3 points from baseline in ESS (60). Different reductions in ESS to assess response, as identified in the literature, were explored in a sensitivity analysis (see Section B.3.8.4).

The IPD from TONES 2 comprised patients with ESS >10 at study baseline and those randomised to the licensed doses of solriamfetol (75 and 150 mg); the mean (SD) baseline ESS for patients with ESS >10 at baseline was [redacted] (see Section B.3.2.1). The analysis focused on the use of the solriamfetol 150 mg IPD, however the 75 mg formulation was considered as a comparator to align with the output from the ITC which accounted for the relative treatment effects.

Figure 16 depicts how the IPD were split into responders and non-responders, and the respective mean change in ESS for each group at week 8, using the 150 mg solriamfetol dose arm as the reference, in line with the outputs of the ITC. Note that the data do not follow a normal distribution; the curve is purely illustrative.

Figure 16. Illustration of IPD for solriamfetol 150 mg



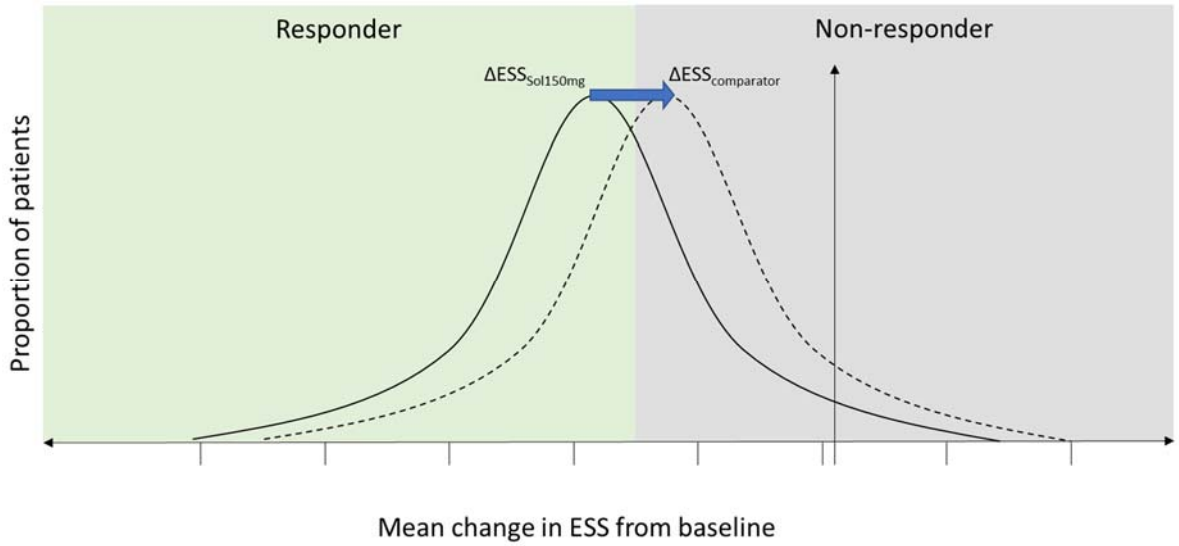
Abbreviations: ESS, Epworth Sleepiness Scale; IPD, individual patient level data.
Δ represents change in ESS from baseline. Dashed vertical line represents mean ESS change for entire arm.
A responder is defined as a patient achieving a reduction in ESS ≥3.

For comparators

To determine the proportion of responders for the comparator treatments, and solriamfetol 75mg, the mean change in ESS relative to solriamfetol 150 mg, as determined in the ITC (see Section B.2.9) was applied to the solriamfetol 150 mg IPD from TONES 2. This created a pseudo-IPD dataset for each comparator, such that for each patient record in the solriamfetol 150 mg data set, the change in ESS from baseline at week 8 was determined, and then for each comparator, the change in ESS relative to the solriamfetol 150 mg dose was applied, to estimate a revised change in ESS from baseline at week 8 for each patient creating a pseudo-IPD dataset for the comparators. The change from baseline was then assessed against the response criteria, as with the original TONES 2 solriamfetol 150 mg IPD, to determine the proportion of responders and non-responders at week 8.

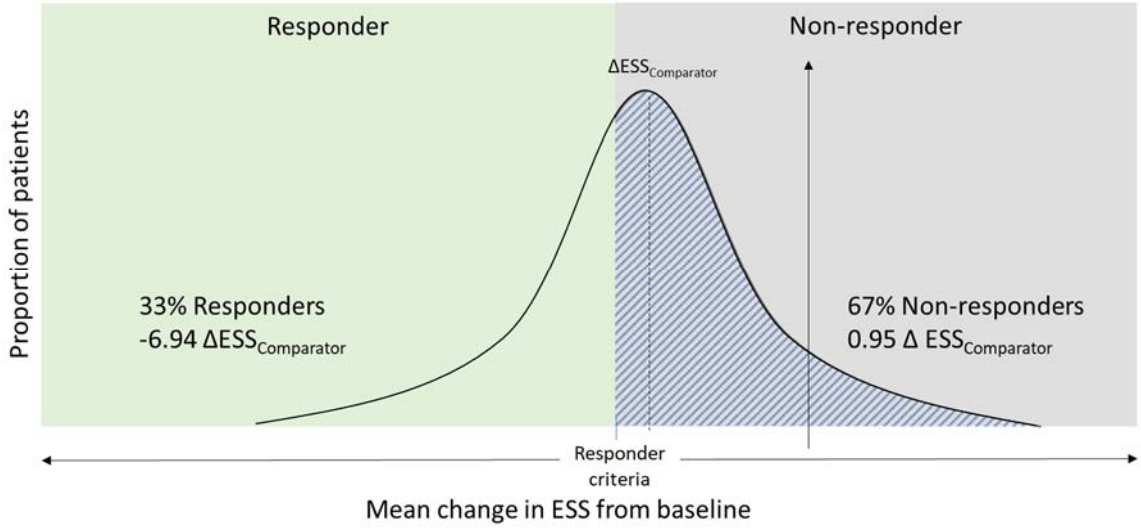
Figure 17 is a graphical illustration of how the solriamfetol 150 mg IPD were transformed, using the mean change in ESS at week 8 for comparators relative to solriamfetol 150mg, to create a pseudo-IPD dataset for each comparator.

Figure 17. Transformation of IPD for comparator



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.

Figure 18. Illustration of pseudo-IPD for comparators



Abbreviations: ESS, Epworth Sleepiness Scale; IPD, individual patient level data.
Δ represents change in ESS from baseline. Dashed vertical line represents mean ESS change for entire arm.
A responder is defined as a patient achieving a reduction in ESS ≥3.

Due to the relatively small sample of solriamfetol 150mg IPD the model utilised bootstrapping methods as detailed by Grey (156), to sample from the IPD. The

model drew a sample of 5,000 patients, with replacement, from the original IPD and each comparator. The clinical output for each sample was then utilised in the model and the associated costs and QALYs for all the products considered were recorded. This resampling process was repeated 1,000 times, with the mean costs and QALYs for all of the repetitions presented as the final base case analysis.

B.3.3.2 Clinical data: Change in ESS

For all patients identified as responders or non-responders at 8 weeks, the change in ESS from baseline was reported and averaged for each outcome to result in different changes in ESS from baseline for responders and non-responders respectively, for each treatment considered. This resulted in a different change in ESS from baseline for responders and non-responders, for each of the treatments considered (see Table 41). As the QoL was derived from the mean change in ESS for each treatment (see Section B.3.4.5), the associated utility of responders and non-responders also varied based on the treatment received.

Table 41. Clinical data utilised in the current model (narcolepsy)

Product, daily dose	Mean ΔESS relative to solriamfetol 150 mg at week 8 (95% CrI)[a]	Absolute ΔESS from baseline[b] (all patients†)	Proportion of responders (ΔESS from baseline ≥3)	Mean ESS in responders	Mean ESS in non-responders
Solriamfetol, 75 mg	−1.80 (−3.46, −0.14)*	-3.20	50%	10.22	17.73
Solriamfetol, 150 mg	Reference product	-5.00‡	65%	9.58	16.72
Pitolisant (≤40 mg)	0.05 (−2.28, 2.38)	-5.05	65%	9.53	16.67
Sodium oxybate, 4.5 g	−2.95 (−5.45, −0.45)*	-2.05	33%	10.15	18.05
Sodium oxybate, 6.0 g	−1.95 (−4.45, 0.56)	-3.05	50%	10.37	17.86
Sodium oxybate, 9.0 g	0.66 (−1.52, 2.82)	-5.66	65%	8.92	16.07

Abbreviations: CrI, credible interval; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness scale; IPD, individual patient data.
Δ represents change in ESS from baseline.
* Change compared to solriamfetol 150 mg (CrI did not cross 0).
†All patients, irrespective of response/non-response; ‡Change estimated via IPD.
a. With regards to the mean change in ESS relative to solriamfetol 150mg; a negative figure means that the comparator is less effective than solriamfetol 150mg with comparative efficacy reducing as this figure moves further from zero. Conversely, a positive figure means that the comparator is more effective than solriamfetol 150 mg with the comparative efficacy increasing as the figure moves further from zero.
b. With regards to the absolute change in ESS from baseline; Patients with EDS will have a high ESS as symptoms improve the ESS will reduce, as such a negative figure demonstrates the improvement in a patient's symptoms. As the figure moves further from zero the less EDS a patient will experience.

The base case analysis assumed that although treatment response would be assessed clinically at week 8, the change in ESS occurred after 1 week of treatment, in line with the rate of response after treatment initiation demonstrated in TONES 2; for responders, the effect on ESS persisted for the duration of the model time horizon whilst a patient remained on therapy.

Within the treatment initiation phase (i.e. the decision tree element), non-responders to treatment were assumed to benefit from any changes they achieved in ESS during the initial 8-week period; this was to reflect the small benefit that non-responders may achieve during an initial treatment period despite not achieving the clinically defined response criteria (≥3 point reduction in ESS), and is reflective of changes in ESS observed in TONES 2. After the patient's assessment of treatment response at 8 weeks, these non-responders were assumed to cease treatment, and revert to their baseline (pre-treatment) ESS. Any patients who were responders but who subsequently discontinued treatment (i.e. in the Markov element) were also assumed to cease treatment and revert to their baseline (pre-treatment) ESS.

The randomised withdrawal phase of TONES 5 (see Section B.2.6.3.3) demonstrates that upon discontinuation of solriamfetol, patients experienced increased EDS within 2-weeks of treatment discontinuation, with mean ESS trending towards baseline. This indicates that once patients are withdrawn from treatment, the treatment-related effects on EDS diminish rapidly and their pre-treatment levels of EDS return. This is consistent with clinical expectations, as none of the treatments for EDS are disease modifying of the underlying narcolepsy and the half-life for solriamfetol and the comparators are all under 12 hours with complete elimination expected within days (63, 64, 66-68). As such, and for simplicity, the current analysis assumed that the return to baseline ESS was immediate.

B.3.3.3 Adverse events

In TONES 2, AEs with an incidence ≥5% (Table 33) in the solriamfetol 75 and 150 mg arms included headache (respectively, 23.7% and 10.2%), nausea (10.2% and 5.1%), decreased appetite (both 8.5%), nasopharyngitis (13.6% and 8.5%%), dry mouth (6.8% and 5.1%), and anxiety (5.1% and 1.7%). Most AEs occur early in the course of treatment (e.g. within the first 1–2 weeks), are self-limiting, and

generally resolve quickly (see Section B.2.9.4 and Appendix C). The KOL Clinical Practice Interviews confirmed that for the existing pharmaceutical-based treatments for EDS in narcolepsy, any treatment-related AEs are unlikely to require substantial intervention, thus for the purposes of this analysis only the impact of discontinuation due to AEs are considered.

B.3.3.4 Discontinuation – Due to AEs

Treatment initiation phase: In TONES 2, the incidence of AEs that led to study drug withdrawal and discontinuation from the study were low: 1.7%, 1.7% and 5.1% for placebo, solriamfetol 75 mg, and solriamfetol 150 mg, respectively. The IPD therefore assumed that patients who discontinued due to AEs did not record any change in ESS from baseline, such that on assessment of response they were considered non-responders. This approach assumed that the rate of discontinuation due to AEs during the initiation phase was equivalent for the treatments considered within the analysis; this is supported by the ITC of discontinuation due to AEs (see Section B.2.9, and Appendix C, Figures 7 to 9) which demonstrated no statistically significant differences in the relative rate of discontinuations due to AEs between solriamfetol and the comparators defined in the company submission problem.

Maintenance treatment phase: In TONES 5 discontinuation due to AEs (for all doses including the unlicensed 300 mg dose) was observed in 23/226 (10.2%) participants with narcolepsy, however, 56.8% of all AEs occurred within the first 4 weeks of treatment (85). For the purposes of the current analysis, and assuming that the rate of discontinuations due to AEs reported at week 4 in TONES 5 is approximate to those that occurred during the 8 week modelled initiation phase (i.e. the decision tree component), it was assumed that the annual rate of AE-related discontinuations after titration is 4.4% (i.e. 43.2% of 10.2%). As before, this is assumed to be equivalent for all treatments within the analysis. However, given that the TONES 5 study design utilised a combined solriamfetol arm (included the unlicensed 300 mg dose), this is likely to be an overestimated rate of discontinuations due to AEs.

B.3.3.5 Discontinuation – Loss of response

In TONES 5, study withdrawal due to loss of response was observed in 39/226 (17.3%) participants with narcolepsy (85). As with discontinuation due to AEs, a proportion of these discontinuations would have occurred during the initiation phase (i.e. the decision tree component). 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 (77); 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. No longer term data (beyond 1 year) are available for solriamfetol nor the comparators, therefore this analysis assumed the same rate of discontinuation due to loss of response and discontinuations beyond year one for all treatments. This assumption was explored in sensitivity analysis (Section) B.3.8.4.

B.3.3.6 Mortality

Mortality impact is modelled as described in Section B.3.2.3. Patients with EDS are more prone to accidents and more susceptible to illness than people without EDS, and as a consequence patients with EDS may have increased risk of mortality (157). However, with the exception of the association between EDS and an increased risk of RTA (which this analysis did not consider, see Section B.3.2), no other direct evidence was identified that could quantify any increased risk of mortality associated with EDS. This analysis therefore conservatively excluded any excess mortality that may be associated with non-responders to treatment who would consequently have a greater level of EDS compared with responders whose EDS is controlled.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from solriamfetol clinical trials

EQ-5D-5L was collected during the TONES 2 trial to measure the QoL of patients. However, this TONES 2 EQ-5D dataset is not being used to directly inform the current cost-effectiveness analysis. The rationale as to why the TONES 2 EQ-5D dataset is not considered an appropriate choice for the model is described below.

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, as reported in Section B.2.6.1 In contrast for EQ-5D-5L there were no meaningful trends observed in domain scores, utility index scores or VAS scores, for reasons that are uncertain (See Section B.2.6.1.8).

In this respect, the results observed on the EQ-5D are inconsistent with the other outcome measures in the TONES 2 study, and not consistent with other available data on QoL impacts of narcolepsy measured using tools other than EQ-5D; in one study for example, patients with narcolepsy in the UK had lower QoL compared with matched normative data and CPAP-treated patients with OSA, as measured using SF-36 and FOSQ (25).

A number of hypotheses can be proposed for this anomaly on analysis of the TONES 2 EQ-5D data, some of which relate to the EQ-5D as a generic tool and others related to the population in the trial:

- EQ-5D does not contain a domain to specifically examine sleep or wakefulness. Therefore, it is likely that important aspects of a patient's QoL are not taken into account when using the EQ-5D. Yang et al (158) investigated the impact of including a "Sleep" domain in the EQ-5D and found that it did not improve the predictive power of EQ-5D to value QoL. However, it is important to note that this explored domain was sleep and not EDS. The impact of sleep quality has the potential to impact long term outcomes as well as in some cases impacting EDS and short term QoL; therefore, whilst important for overall health, it is not necessarily surprising that it did not have an impact on EQ-5D. It should be noted that the absence of a benefit seen by adding a "Sleep" domain in this paper is not confirmation that EQ-5D is already a suitable tool to monitor the QoL impact of sleep disorders, but rather that the proposed addition did not improve its sensitivity. EDS on the other hand is known to have a substantial impact on QoL, which does not appear to be fully valued by EQ-5D. The impact of including an EDS domain has not yet been examined.
- EQ-5D does not include a domain to specifically examine relationships with family and friends. This is the most frequently mentioned impact on QoL overall

in the general population (159) and without its inclusion in the EQ-5D there is potential for a ceiling effect when examining social isolation (160). Around 65-66% of patients with narcolepsy in the UK report difficulties maintaining friendships or building and maintaining relationships, and 86% said their narcolepsy affected the time they spent with their friends (26).

- Patients showed a limited disutility on EQ-5D at trial baseline (Mean utility index [redacted] for control, 75 mg and 150 mg solriamfetol (76), with [redacted] of patients scoring as 1.0), which is not in keeping with all known impacts of EDS on patients with narcolepsy (See Section B.1.3). As such demonstrating an improvement on EQ-5D with treatment from a high baseline is challenging. TONES 2 is not the first study in a narcolepsy population that would suggest that EQ-5D may not adequately capture the problems associated with the disease; Dodel et al (161), in a German population, showed that QoL was reduced in narcolepsy versus the general population when measured across all 8 domains of the SF-36 but QoL was comparable using EQ-5D utilities.
- Patients with narcolepsy, in living with a chronic condition will adapt their lifestyle and usual activities. The impact of adaptation on a patient's perceived QoL is likely to be most apparent when assessing the impact of EDS, for which it would be the usual activities domain of EQ-5D that would drive many of the changes observed. Once a patient has adapted their lifestyle to their EDS, they may then re-define what their usual activities are from their perspective, such that when asked regarding usual activities in EQ-5D, there is apparently little impairment. In addition, there may be many other activities an adapted patient would wish to do, that would significantly improve their QoL, but their disease prevents them from doing it – EQ-5D does not test this specific scenario of adapted disutility. The impact of adaptation may be apparent in TONES 2; although in the UK, the vast majority (88%) of patients report that narcolepsy affects the activities they do (26), around 60% of patients reported no or only slight problems in the usual activities domain at baseline in TONES 2 (76).
- Depression in the trial population is around 25% (76), which, if effectively treated might have reduced the impact of a disutility on this domain. Patients with narcolepsy and depression have significantly worse QoL, compared with patients with narcolepsy but without depression (37).

- In TONES 2 the majority of patients (>95%) were rated by clinicians as being moderately, markedly, severely or among the most extremely ill (CGI-s), yet [redacted] of all TONES 2 patients had an EQ-5D utility score of 1 at baseline. Given that this is also a population who have an ESS score of ≥10, the proportion of patients with a utility of 1 in the study would appear high. This is even more evident when put in the context of data from the EU5 National Health and Wellness Survey (NHWS) comprising of patients with narcolepsy or OSA (see Appendix M), where approximately two-thirds of patients (n=1,557/2,348) were in the normal ESS range (≤10) and therefore a utility score of 1 might be more appropriate; however, approximately [redacted] of this population had a baseline utility score of 1. This apparent contrast between the assessment of disutility by EQ-5D in TONES 2, as compared to assessment by the NHWS data set supports the proposal that the TONES 2 EQ-5D dataset is not an appropriate choice for the model.
- The TONES 2 population comprised patients from the US, Canada and Europe, and geographical variations may be apparent when considering the impact of EDS on QoL and utility. Interaction tests carried out on EQ-5D-5L data for each of the five domains in US vs non-US patients in TONES 2 show a difference in the slope between the two populations (see Appendix D for results). Differences between populations across these geographies, which may affect the sensitivity of EQ-5D to detect the impact of EDS, include:
  - Compared with Europe, there are fewer restrictions in the US related to driving for patients with EDS and therefore there may be less potential to detect a negative impact on the patient's usual activities domain. Examination of TONES 2 patient level data at baseline shows that a 1 point change in ESS has just over half of the impact on the individual domain score for usual activities in the US versus those outside the US (including Europe).
  - In the US the mobility domain responses do not change with ESS score, whereas outside the US scores appear to get worse with increasing ESS. This could be due to the lower need to travel by foot in the US (162) and a patient's EDS could reasonably impact their energy levels and how able they feel to walk the longer distances typically travelled on foot outside the US.

- The pain & discomfort domain score changes approximately 4 times as much in patients outside the US per point of ESS than for US patients. There is a link between pain and tiredness (163), and it is understood that management of pain is a matter of course in the US (164, 165), compared with the outside the US. It is therefore likely that more patients will receive a medication when proactively asked (such as in the US) than if the onus is on the patient to bring this up themselves (such as outside the US) with the physician.
- The potential differences between US and non-US populations with EDS appears to be borne out in real world evidence; US data from the NHWS reported by Stepnowsky 2019 (166) shows a utility difference between OSA patients with EDS and without EDS of 0.65 and 0.69 (using SF-36), respectively, compared with 0.62 and 0.71 (using EQ-5D), respectively, in a corresponding NHWS dataset in the EU5 (including OSA and narcolepsy patients; see Appendix M).

These factors strongly support the assertion that EQ-5D may under value the improvement in health state achieved through treating EDS in narcolepsy with solriamfetol, of which some are specifically related to the population seen in TONES 2. Accordingly, this supports the decision to not consider the overall TONES 2 EQ-5D dataset in the cost-effectiveness analysis.

Although a potential option would have been to consider the European patient dataset from the TONES 2 trial, patient numbers in this subset were very small (n=44/236 across the entire trial) and thus preclude any meaningful analyses.

B.3.4.2 Health-related quality-of-life studies

In the absence of appropriate trial-based EQ-5D data for incorporation in the cost-effectiveness analysis, an SLR was conducted to identify studies reporting on the HRQoL of patients with narcolepsy. Full details of the methodology and results of the studies identified are presented in Appendix H. In total, eight records for seven unique studies were identified which reported HSUVs for patients with narcolepsy, one of which was conducted from a UK perspective (PenTAG – Lanting 2014 (133)) and the remainder from a European (27, 132, 161, 167, 168) or US perspective (44,

169). Although not formally searched for in the HRQoL SLR, the three narcolepsy HTA submissions identified during the cost-effectiveness SLR (see Section B.3.1; two to SMC (135, 137) and one to CADTH (136)) were cross-checked for relevant utility values. The sources of utility data were unclear across all three submissions due to limited reporting in the submission documents, and no utility values were reported. As described in Section B.3.1, NICE TA139 for CPAP in the treatment of OSAHS (138, 139) was also interrogated for relevant information on utility values and related methodological details.

The two UK-based analyses – PenTAG (Lanting 2014 (133)) and the York assessment group model of NICE TA139 (McDaid 2007 (138, 139)) – both used the same approach to quantify QoL:

- In TA139, the McDaid 2007 used the surrogate end point of ESS score as a proxy for differences in utility for patients with OSAHS (139). Three sets of individual patient-level data (two measuring ESS and SF-36 profile in the same patients (170, 171) and one that measured ESS, SF-36 profile and EQ-5D-3L data in the same set of patients (153)) were used to map ESS scores to EQ-5D-3L and SF-6D values (based on tariffs published by Brazier 2002 (172) and Dolan (173)) using a simple linear regression analyses.[s] The results of this process indicated that a unit fall in ESS score is associated with an increase in utility of 0.0097 (95% CI: 0.0019, 0.0175) based on EQ-5D-3L (n=94) and of 0.0095 (95% CI: 0.0070, 0.0123) based on SF-6D (n=294) (Table 42).
- In their study, PenTag (Lanting 2014 (133)) assessed the cost-effectiveness of sodium oxybate for narcolepsy. In the absence of appropriate data for the change in utility experienced following response to sodium oxybate treatment, Lanting 2014 adopted the same approach taken by McDaid 2007 in TA139, assuming a relationship between EQ-5D and improvements in ESS scores. This EQ-5D utility change was then applied to responders, based on the mean ESS improvement observed with sodium oxybate treatment (ESS score change = 4). Although the McDaid algorithm was based on treatment for OSAHS, Lanting 2014 commented that there was no reason to believe that the

[s] Citation details for patient-level data and tariffs as per those listed by McDaid et al (139).

relationship between ESS and utility change is disease specific, and concluded that the McDaid algorithm was applicable in the narcolepsy population (133).

Both of these studies demonstrate that the principle of a statistical link between ESS and EQ-5D has been established and used in cost-effectiveness analyses to support treatments for sleep disorders. Of particular note is the development of this methodology by the York assessment group as part of a NICE TA139 (139).

Table 42. Coefficients from utility analysis from NICE TA139 (139)

Utility	Coefficient	95% Confidence interval	
		Low	High
OLS model for utility based on SF-6D (n=294)			
ESS	-0.0095213	-0.0122512	-0.0067915
Baseline ESS	0.0050331	0.0026791	0.0073871
Constant	0.8067555	0.7840945	0.8294265
OLS model for utility from EQ-5D (n=94)			
ESS	-0.0096984	-0.0175364	0.0018604
Baseline ESS	0.0029526	0.0037382	0.0096435
Constant	0.8925207	0.8357052	0.9493363

Abbreviations: EQ-5D, 5 dimension EuroQol; ESS, Epworth Sleepiness Scale; SF-6D, 6 dimension Short Form 36-item Health Survey; NICE, National Institute for Health and Care Excellence; OLS, ordinary least squares; OSA, obstructive sleep apnoea.

B.3.4.3 Mapping

In the absence of suitable trial-based EQ-5D utilities from TONES 2 (as outlined in Section B.3.4.1), and based on the studies identified by the SLR (Section B.3.4.2), a potential approach to modelling utilities is to align with the ESS to EQ-5D mapping exercise taken in TA139 (McDaid approach (139)) and subsequently adopted by Lanting 2014 (133). Following similar methodology, two options were considered for inclusion in the current cost-effectiveness analysis, as described below:

- De Novo analysis of NHWS data
- McDaid algorithm

The McDaid algorithm

The McDaid algorithm was developed to inform TA139 in assessing CPAP for OSAHS (139), and subsequently used by Lanting 2014 in assessing cost-effectiveness of sodium oxybate for narcolepsy (133). The EQ-5D-ESS algorithm

was developed using a sample of 94 OSA patients (no narcolepsy patients were included). It uses a linear regression model, and whilst a test was performed to check for evidence of a change of slope, no evidence was found to support this effect. This is considered likely down to the small sample size.

De Novo analysis of NHWS data

The NHWS is a self-administered, internet-based questionnaire from a sample of adults (aged 18 years or older) in several countries, including the EU5 (UK, France, Germany, Italy and Spain). The NHWS is designed to reflect the general population of each country surveyed. Potential respondents were identified primarily through participation in opt-in online survey panels, with stratified random sampling within the survey panel to ensure country-specific representativeness in terms of age and gender. The 2016-2017 EU5 NHWS included data from 123,214 respondents.

A de novo analysis was conducted based on a subset of 2,348 respondents across the EU5 who self-reported experiencing OSA and/or narcolepsy in the past 12 months, self-reported a diagnosis of OSA and/or narcolepsy and completed the ESS (described in more detail in Appendix M).

The analysis of EQ-5D and ESS showed no interaction in slope between narcolepsy and OSA, in line with the expectations of Lanting 2014 (133) that the disease would likely not change the impact of the EDS. However, the fact that this has been tested for in this dataset gives the NHWS analysis greater credibility for use in a narcolepsy population compared to a dataset derived from OSA alone (i.e. McDaid). As a multivariate analysis, likely confounding variables could also be controlled for, again increasing its credibility.

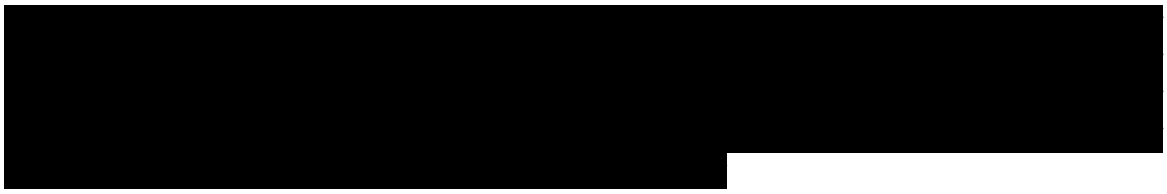
Across the full population (narcolepsy and OSA), the analysis shows a similar, if slightly shallower slope versus the McDaid analysis. In contrast to McDaid which used a simple linear regression, a segmented piecewise model proved to have the best fit, suggesting a different ‘shape’ to the overall utility function (see Figure 19 for relative differences between McDaid and NHWS). This showed the utility slope for ESS scores >11 to be steeper than for ESS scores ≤11. This intrinsically makes clinical and biological sense, given the proximity of the break point of 11.29 on the ESS from this analysis to the widely accepted top end of the ‘normal’ range

(ESS=10) (See Table 6); i.e. once patients achieve normal ESS or close to normal ESS, QoL doesn't improve notably as patients become more 'normal'.

Figure 19. Relationship between EQ-5D and ESS score based on McDaid and NHWS algorithms

Abbreviations: Abbreviations: EQ-5D-5L, 5-dimension, 5-level EuroQol; ESS, Epworth Sleepiness Scale; NHWS, National Health and Wellness Survey.
To allow for a comparison of the overall difference between the slopes of NHWS and McDaid across the range of ESS severities, the NHWS slopes were applied using the constant of McDaid.

The final NHWS mapping algorithm for estimating EQ-5D-3L utilities takes the following form:



For several of the covariates; Charlson Comorbidity Index Quan score (CCIQuan), Marital status, income, BMI, smoking status, alcohol consumption and exercise, there is no corresponding data from TONES 2 nor any data available to populate this to reflect the UK population being considered. As such, the sample average from the NHWS dataset has been used (As described in Appendix M).

There are limitations to this analysis in that there may be confounding variables that might not have been captured. Two additional factors may also explain the slightly shallower overall slope compared to McDaid:

- **Income** – patients on an income of £/€20,000–£/€40,000 had an additional utility of 0.0496 compared to those on <£/€20,000. There is little further improvement over £/€40,000. This suggests that the greatest improvement in QoL is observed in moving patients away from low income and towards median national income. Given the impact that EDS has on work, it is entirely possible that improving a patient's EDS could also improve a patient's QoL via their income.
- **Exercise** – A patient able to do a moderate amount of exercise has a 0.106 improvement in utility over a patient who is not able to do this. It is feasible that a patient who feels less sleepy might feel more able to take part in regular exercise and could further improve their quality of life.

Despite the limitations of EQ-5D in general (which could mean that any EQ-5D dataset could undervalue the impact on QoL of EDS), it is felt that on the balance of these arguments the NHWS is the most robust of the ex-US datasets, and this has been chosen as the base case source of utility data for this submission, with scenario analyses using the McDaid algorithm.

B.3.4.4 Adverse reactions

As described in Section B.3.3.3, incidence of AEs has not been considered in the base case analysis and thus utility decrements resulting from AEs are also not modelled.

B.3.4.5 HRQoL data used in the cost-effectiveness analysis

The HRQoL of the cohort over the time horizon of the model was considered by assigning a utility value to the treatment adjusted ESS via the NHWS mapping algorithm detailed in Section B.3.4.3.

Patients entered the model with a baseline ESS score (derived from the mean solriamfetol 150 mg IPD), and this was used to calculate an associated utility value using the NHWS mapping algorithm (see Section B.3.4.3). Patients were assessed to be responders or non-responders (see Section B.3.3.2) and attributed a change in ESS from baseline, which was then used to estimate the treatment-related ESS score. This treatment adjusted ESS score was again used to estimate a treatment

related utility using the NHWS mapping algorithm. In the base case it was assumed that the change in ESS, for responders and non-responders, occurred within 1 week of treatment initiation, for all treatments, and persisted until response was assessed clinically at week 8.

At this point, those patients that were classified as responders remained on treatment for the duration of the model time horizon, unless they discontinued therapy, and therefore maintained the ESS associated with the specific treatment's response. The utility was re-estimated in each cycle to account for the age covariate in the NHWS mapping. Those patients that did not achieve response, or discontinued, were assumed to revert to the mean baseline ESS for the remainder of the model time horizon. Again, the utility value was re-estimated in each cycle to account for the age covariate in the NHWS mapping.

Table 43. Mean ESS in responders and non-responder and the associated utilities

Product, daily dose	Mean ESS in responders	Mean utility of responders up to week 8	Mean ESS in non-responders	Mean utility non-responders up to week 8
Solriamfetol, 75 mg	10.22	0.682	17.73	0.591
Solriamfetol, 150 mg	9.58	0.683	16.72	0.605
Pitolisant (≤40 mg)	9.53	0.683	16.67	0.605
Sodium oxybate, 4.5 g	10.15	0.682	18.05	0.587
Sodium oxybate, 6.0 g	10.37	0.681	17.86	0.590
Sodium oxybate, 9.0 g	8.92	0.685	16.07	0.613

Abbreviations: ESS, Epworth Sleepiness Scale.

Table 41 shows the mean ESS in responders and non-responders, as derived from the IPD for solriamfetol and pseudo-IPD (see Section B.3.3.1) for each comparator treatment. These values were then used with the NHSW mapping to estimate the corresponding utility value. Patients who had not achieved response were assumed to return to the baseline ESS and corresponding utility. Those patients who responded were assumed to maintain the treatment-related ESS but as detailed previously, the associated utility values were re-estimated each cycle to account for the age covariate in the NHSW mapping.

An alternative scenario using the McDaid 2007 mapping algorithm (Section B.3.8.4) is also considered.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted but did not identify any studies for healthcare resource usage or costs for patients with narcolepsy in the UK. Full details of the methods and results of studies reporting cost and resource use data are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

All treatments considered in the model were consistent with the dosing recommendations of their respective marketing authorisations (66, 67). All prices were from the National Drug Tariff (154), with the exception of solriamfetol (Table 44). The analysis assumed that treatment initiation and assessment at week 8 was identical for all therapies considered; this was confirmed by KOL Clinical Practice Interviews (2) and as such, the cost of initiation and assessment of response was excluded from the analysis.

Table 44. Drug acquisition costs: primary treatments

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 (174)	4.5mg 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 (175)	500 mg/ml	180 ml	360.00	0.004*	4,500 6,000 9,000	18.00 24.00 36.00

* price per mg, equivalent to £4.00 per gram.

Solriamfetol

Solriamfetol is available as 75 mg and 150 mg film-coated tablets, and the recommended starting dose is 75 mg once daily, upon awakening. Treatment should be initiated by a clinician experienced in the treatment of sleep disorders. 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 75 mg dose may be titrated to the 150 mg dose by doubling the dose after an interval of at least 3 days (see

Appendix C). Due to the short duration of titration, and because patients can initiate on the 150 mg dose, this analysis conservatively assumed that throughout the first 8 weeks of the model, patients received the cost of the highest dose that they titrated to, equating to:

- An 8-weekly cost of £355 and £497 for the 75 mg and 150 mg respectively.
- For those that continue therapy beyond 8 weeks, a weekly cost of £44 and £62 is assumed for the 75 mg and 150 mg daily doses, respectively.

The dosing in TONES 2 was determined by randomisation and in TONES 5 patients were protocol-driven to titrate to the highest tolerated dose, thus these studies do not provide a representative breakdown of how solriamfetol would be administered in practice or the final dose distribution that would be observed. The current analysis considered each dose separately, and a combined analysis is also presented using an assumed 50/50 split of the two final doses, based on the current prescribing data available from the US; this is also varied in sensitivity analysis.

Pitolisant

Pitolisant is available as 4.5 mg tablets (which contain 5 mg of pitolisant hydrochloride equivalent to 4.5 mg of pitolisant) and 18 mg tablets (which contain 20 mg of pitolisant hydrochloride equivalent to 18 mg of pitolisant). Treatment should be initiated by a clinician experienced in the treatment of sleep disorders. Pitolisant should be used at the lowest effective dose, depending on individual response and tolerance, without exceeding 36 mg per day (67). Pitolisant should be titrated as follows:

- Week 1: initial dose of 9 mg (2×4.5 mg tablets) per day.
- Week 2: the dose may be increased to 18 mg (1×18 mg tablet) per day or decreased to 4.5 mg (1×4.5 mg tablet) per day.
- Week 3: the dose may be increased to 36 mg (2×18 mg tablets) per day.

At any time, the dose can be decreased (down to 4.5 mg per day) or increased progressively (up to 36 mg per day) according to response. The total daily dose should be given as a single dose in the morning during breakfast.

The ITC evidence (see Section B.2.9) did not allow for a specific dose of pitolisant to be considered, due to the manner in which the available RCTs reported data (doses

were reported as "≤40 mg/day"). However, in NICE ES8, the manufacturer (Lincoln Medical Ltd) estimated that approximately one third of patients would be maintained on 18 mg per day and two thirds on 36 mg per day (3). Based on the titration information and the assumptions on final dosing, the estimated cost of the first 8 weeks of treatment was assumed to be £1,181.44 per patient and in those who continue therapy a weekly cost of £120.56 was assumed (Table 45). The proportion of patients on 18 mg and 36 mg daily doses was considered in sensitivity analysis.

Table 45. Pitolisant titration and maintenance dosing

	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
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

Sodium oxybate

Sodium oxybate is available as an oral solution with each mL of solution containing 500 mg of sodium oxybate. The recommended starting dose is 4.5 g per day sodium oxybate divided into two equal doses of 2.25 g per dose. The dose should be titrated to effect based on efficacy and tolerability up to a maximum of 9 g per day divided into two equal doses of 4.5 g per dose by adjusting up or down in dose increments of 1.5 g per day (i.e. 0.75 g per dose). A minimum of one to two weeks is recommended between dose increments (66).

The ITC considered three separate daily doses of sodium oxybate: 4.5 g, 6.0 g and 9 g. For the purposes of this analysis it was conservatively assumed that a patient would take two weeks between dose titrations and as such, the associated 8-week costs were estimated to be £1,008, £1,302 and £1,764 for the 4.5 g, 6.0 g and 9 g

daily doses respectively, including the cost of titration. For those that continued therapy a weekly cost of £126, £168 and £252 was assumed for the 4.5 g, 6.0 g and 9 g daily doses respectively.

As with solriamfetol, there are no available data on the proportion of patients who would reach the respective final doses for sodium oxybate. For the purposes of this analysis the doses were presented individually but a weighted average for all sodium oxybate doses was also presented for consideration using a conservative equal split across the three formulations, equivalent to an average daily dose of 6.5 g. This is conservative compared with the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology which reports a defined daily dose for sodium oxybate of 7.5 g (176).

B.3.5.2 Health-state unit costs and resource use

Typically, after treatment initiation and assessment of treatment response, patients with narcolepsy are reviewed by a specialist every 3–6 months either during regular follow-up clinics, or via telephone. The treatments considered in the analysis help to manage the symptoms of EDS in patients with narcolepsy and are not treatments for the underlying narcolepsy. Based on the KOL Clinical Practice Interviews (2), patients are followed-up at regular intervals for the management of their narcolepsy, and any treatment assessment or treatment-related monitoring required would occur during these same visits; thus there is no evidence to suggest that a reduction in EDS would result in an associated reduction in costs and therefore this analysis conservatively assumes that there are no cost offsets associated with improvements in EDS.

As previously noted, all AEs in TONES 2 and across the studies for the comparator products were transient, therefore in the base case analysis, treatment-related AEs that did not lead to discontinuation were not considered. Furthermore, they were also comparable between all comparators in the main analysis. However, a general practitioner (GP) contact (at £37 per contact) has conservatively been included for completeness for all AEs leading to discontinuation in the base case (155).

It should be noted that it has not been possible to quantify the impact of adverse events in methylphenidate/dexamfetamine due to the lack of evidence.

B.3.5.3 Miscellaneous unit costs and resource use

Not applicable. Based on the KOL Clinical Practice Interviews, patients with narcolepsy are monitored during regular follow-up visits, and therefore this analysis conservatively assumes that there are no additional costs beyond those that would be incurred during regular visits (2).

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 46 provides a list of variables and inputs used in the base case analysis.

Table 46. Parameters used in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
Discount rate: Costs	3.5%	0.0% - 6.0% (Not varied)	B.3.2.5
Discount rate: Outcomes	3.5%	0.0% - 6.0% (Not varied)	
Average age at baseline	38.0	24.9 - 51.0 (Not varied)	B.3.2.1
Proportion of cohort that are female	70.4%	48.0% - 68.1% (Beta)	
Excess narcolepsy mortality - Male	1.6	1.4 - 1.7 (Normal)	B.3.2.4
Excess narcolepsy mortality - Female	1.4	1.3 - 1.6 (Normal)	
Solriamfetol - 75 mg: Pack size	28.0	28.0 - 28.0 (Not varied)	B.3.5.1
Solriamfetol - 150 mg: Pack size	28.0	28.0 - 28.0 (Not varied)	
Pitolisant 4.5 mg: Pack size	30.0	30.0 - 30.0 (Not varied)	
Pitolisant 18 mg: Pack size	30.0	30.0 - 30.0 (Not varied)	
Sodium Oxybate: Pack size	180.0	180.0 - 180.0 (Not varied)	
Dexamfetamine: Pack size	30.0	30.0 - 30.0 (Not varied)	
Methylphenidate: Pack size	30.0	30.0 - 30.0 (Not varied)	
Solriamfetol - 75 mg: Pack price	£177.52	£177.52- £177.52 (Not varied)	
Solriamfetol - 150 mg: Pack price	£248.64	£248.64- £248.64 (Not varied)	
Pitolisant 4.5 mg: Pack price	£310	£310 - £310 (Not varied)	
Pitolisant 18 mg: Pack price	£310	£310 - £310 (Not varied)	
Sodium Oxybate: Pack price	£360	£360 - £360 (Not varied)	
ESS => EQ-5D: McDaid - Constant	0.893	0.836 - 0.949 (Normal)	Table 42
ESS => EQ-5D: McDaid - ESS	-0.010	-0.018 - -0.002 (Normal)	
ESS => EQ-5D: McDaid - Baseline ESS	0.003	-0.004 - -0.010 (Normal)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
Baseline ESS - Solriamfetol 150 mg	-5.0	-8.5 - -1.5 (Not varied directly)	B.3.3.2
Change in ESS relative to Sol 150 mg: Sol 75 mg	-1.797	-3.456 - -0.137 (Normal)	
Change in ESS relative to Sol 150 mg: Pitolisant	0.050	-2.279 - 2.377 (Normal)	
Change in ESS relative to Sol 150 mg: Sodium Oxybate 4.5 g	-2.946	-5.448 - -0.447 (Normal)	
Change in ESS relative to Sol 150 mg: Sodium Oxybate 6 g	-1.946	-4.451 - 0.558 (Normal)	
Change in ESS relative to Sol 150 mg: Sodium Oxybate 9 g	0.656	-1.518 - 2.832 (Normal)	
Discontinuation - LoE (Year 1): Sol 150 mg	10.9%	8.7% - 13.1% (Beta)	B.3.3.5
Discontinuation - LoE (Year 1): Sol 75 mg	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year 1): Pitolisant	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year 1): Sodium Oxybate 4.5 g	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year 1): Sodium Oxybate 6 g	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year 1): Sodium Oxybate 9 g	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year n): Sol 150 mg	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year n): Sol 75 mg	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year n): Pitolisant	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year n): Sodium Oxybate 4.5 g	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year n): Sodium Oxybate 6 g	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - LoE (Year n): Sodium Oxybate 9 g	10.9%	8.7% - 13.1% (Beta)	
Discontinuation - TEAEs (Year 1): Sol 150 mg	4.4%	3.5% – 5.3% (Beta)	B.3.3.4

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
Discontinuation - TEAEs (Year 1): Sol 75 mg	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year 1): Pitolisant	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year 1): Sodium Oxybate 4.5 g	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year 1): Sodium Oxybate 6 g	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year 1): Sodium Oxybate 9 g	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year n): Sol 150 mg	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year n): Sol 75 mg	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year n): Pitolisant	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year n): Sodium Oxybate 4.5 g	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year n): Sodium Oxybate 6 g	4.4%	3.5% – 5.3% (Beta)	
Discontinuation - TEAEs (Year n): Sodium Oxybate 9 g	4.4%	3.5% – 5.3% (Beta)	
Cost of discontinuation - TEAEs	£37	£30 - £44 (Gamma)	B.3.5.2
Dosing: Pitolisant 18 mg (Weeks 3 - 8)	33.3%	0.0% - 100.0% (Beta)	B.3.5.1
Dosing: Pitolisant 18 mg (Week 8+)	33.3%	0.0% - 100.0% (Beta)	
NHWS mapping - Constant coefficient	[redacted]	[redacted]	B.3.4.3
NHWS mapping - ESS Score: 0-11 coefficient	-0.002631	[redacted]	
NHWS mapping - ESS Score: 12-14 coefficient	-0.013089	[redacted]	
NHWS mapping - SA w/o Narc coefficient	[redacted]	[redacted]	
NHWS mapping - SA w Narc coefficient	[redacted]	[redacted]	
NHWS mapping - Age coefficient	[redacted]	[redacted]	
NHWS mapping - CCIQuan coefficient	[redacted]	[redacted]	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
NHWS mapping - Female coefficient	[redacted]	[redacted]	
NHWS mapping - Married coefficient	[redacted]	[redacted]	
NHWS mapping - Medium Income coefficient	[redacted]	[redacted]	
NHWS mapping - High Income coefficient	[redacted]	[redacted]	
NHWS mapping - BMI coefficient	[redacted]	[redacted]	
NHWS mapping - Former Smoker coefficient	[redacted]	[redacted]	
NHWS mapping - Current Smoker coefficient	[redacted]	[redacted]	
NHWS mapping - Alcohol coefficient	[redacted]	[redacted]	
NHWS mapping - Exercise coefficient	[redacted]	[redacted]	

Abbreviations: BMI, body mass index; CCIQuan, Charlson Comorbidity Index (calculate using the Quan 2011 scoring algorithm (177)); CI, confidence interval; ESS, Epworth Sleepiness Scale; EQ-5D, 5 dimension EuroQol; LoE, loss of efficacy; SA, sleep apnoea; SF-6D, 6-Dimension Short Form 36 Health Survey; TEAE, treatment emergent adverse event.

B.3.6.2 Assumptions

Table 47 provides an outline of the main assumptions of the economic model.

Table 47. Assumptions and justifications used in the economic model

Assumption	Brief justification	Reference to section in submission
Model structure		
Response was defined as a change from baseline ESS of 3 or more	Clinicians advised that they do not generally require patients to achieve a pre-specified absolute change in ESS (2), however the literature supports a reduction of between 2-4 points in ESS as being a clinically meaningful change (90-92).	Table 2 B.3.3.1 B.3.8.4
The absolute change in ESS from baseline varied between the treatments and as such the level of response will vary amongst responders.	Response, defined as a 3-point reduction in ESS from baseline, was simply a criterion for continuation of treatment. The absolute change from baseline was the true measure of treatment efficacy. This is reflective of previous economic evaluations include TA139. The impact of a response of 2 or 4 points was assessed in scenario analyses.	B.3.3.1
This analysis did not consider the impact of EDS on RTAs	Although EDS is associated with an increased risk of RTA, narcolepsy is a 'notifiable' medical condition and patients with uncontrolled EDS must surrender their driving license. As such they would not be considered at risk of being involved in an RTA and consequently RTAs were not considered within the analysis.	B.3.2
This analysis did not consider the impact of CVEs.	Previous economic models associated with EDS considered the impact of CVEs using the Framingham risk equation via changes in systolic BP. These relative changes in systolic BP between treatments were small and there is a lack of conclusive evidence linking the treatment related blood pressure changes to CVEs and consequently are not considered within this analysis.	B.3.2
Clinical inputs		
The model used TONES 2 IPD for those patients who received solriamfetol 150 mg and then applied a relative change in ESS to the change from baseline achieved in the IPD.	This approach implicitly assumed that all patients responded equally, irrespective of baseline severity and this was recognised as a limitation of the approach taken. Although there may be a skew in the way data shifted, no other data was identified that could inform such a shift. A scenario analysis evaluated any potential skew and the impact of this on the cost-effectiveness results.	B.3.3.1
When patients stopped treatment, their ESS returned to baseline levels.	The randomised withdrawal phase of TONES 5 demonstrated that when patients cease treatment, there is a rapid increase in EDS, as measured by ESS, suggesting a return towards baseline. As such, this analysis assumed that patients return to	B.3.3.2

Assumption	Brief justification	Reference to section in submission
	their baseline ESS when they stopped receiving an active treatment.	
Treatment related AEs that did not lead to discontinuation were not associated with any costs or disutilities.	All treatment related AEs, not leading to treatment discontinuation, are transient and generally quick to resolve. As AEs are monitored during routine visits they were assumed not to be associated with additional HRU costs, and they have not been considered within the analysis.	B.3.3.4
Utility inputs		
The NHWS mapping algorithm is used to estimated utilities in responders and non-responders	The NHWS represents the largest ex-US dataset of narcolepsy and OSA patients allowing for the most robust elicitation of EQ-5D based utility values linked to ESS, the primary measure of efficacy in the analysis.	B.3.4.5
MRU and cost inputs		
Administration and monitoring costs associated with the pharmacological interventions were excluded from the analysis	All treatments are oral formulation and as all monitoring occurs during regular visits there are no specific monitoring requirements for any of the treatments considered. The analysis assumed that treatment initiation and subsequent assessment at week 8 would be identical for all therapies considered and as such the cost of initiation and assessment of response was excluded from the analysis.	Table 2 B.3.5.2
There were no health state related costs considered within the analysis	This analysis focuses on the treatment of EDS in patients with narcolepsy, and not the underlying narcolepsy itself. Patients are routinely reviewed and monitored by HCPs and based on the KOL Clinical Practice Interviews, the impact of EDS is unlikely to impact the frequency of regular follow-ups. It could be assumed that those patients who do not respond to treatment and continue to experience EDS may require higher healthcare utilisation but there is limited evidence available to quantify this. As a consequence, and for simplicity, this analysis conservatively excludes health state related costs.	B.3.5.2

Abbreviations: AE, adverse event; BP, blood pressure; CVE, cardiovascular events; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness scale; HCP, healthcare practitioner; HCRU, healthcare resource use; IPD, individual patient level data; MRU, medical resource use; NICE, The National Institute for Health and Care Excellence; RTA, road traffic accident; TA, technology appraisal; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case clinical and economic outcomes, generated from the bootstrapped data, are presented in Table 48 with all individual formulations considered. Over the life-time horizon, the two solriamfetol doses demonstrated dominance over the 4.5 and 6 g doses of sodium oxybate and extended dominance over pitolisant. The ICER associated with sodium oxybate 9 g compared to solriamfetol 75 mg is £509,641 (SW quadrant) and compared to solriamfetol 150 mg is £5,521,622 (SW Quadrant) indicated that solriamfetol would be considered cost-effective at both doses. An analysis combining the respective product doses is presented in Table 49. In this scenario, solriamfetol and pitolisant created the cost-effectiveness frontier but the ICER between the two was £367,593 per QALY (SW quadrant) and sodium oxybate was dominated by solriamfetol. Both presentations demonstrated that solriamfetol is the most cost-effective treatment choice.

Clinical outcomes from the model are provided in Appendix J. Disaggregated results of the base-case cost-effectiveness analysis are provided in Appendix J.

Table 48. Base-case results – By dose

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)	ICER versus solriamfetol 150mg (£/QALY)
Solriamfetol 75mg	£5,975 (£5,974 - £5,977)	13.273 (13.270 - 13.275)	42.044 (42.026 - 42.062)					£70,702*
Solriamfetol 150mg	£10,766 (£10,765 - £10,767)	13.341 (13.338 - 13.343)	42.044 (42.026 - 42.062)	£4,791	0.068	£70,702	£70,702	
Sodium Oxybate 4.5g	£11,473 (£11,468 - £11,477)	13.203 (13.201 - 13.206)	42.044 (42.026 - 42.062)	£707	-0.137	Dominated	Dominated	Dominated
Pitolisant 40mg	£20,991 (£20,990 - £20,992)	13.341 (13.338 - 13.344)	42.044 (42.026 - 42.062)	£9,518	0.138	£69,120	Extendedly dominated	Extendedly dominated
Sodium Oxybate 6g	£22,587 (£22,581 - £22,593)	13.272 (13.269 - 13.274)	42.044 (42.026 - 42.062)	£1,596	-0.069	Dominated	Dominated	Dominated
Sodium Oxybate 9g	£43,532 (£43,530 - £43,534)	13.346 (13.344 - 13.349)	42.044 (42.026 - 42.062)	£20,945	0.075	£280,171	£509,641	£5,521,622*

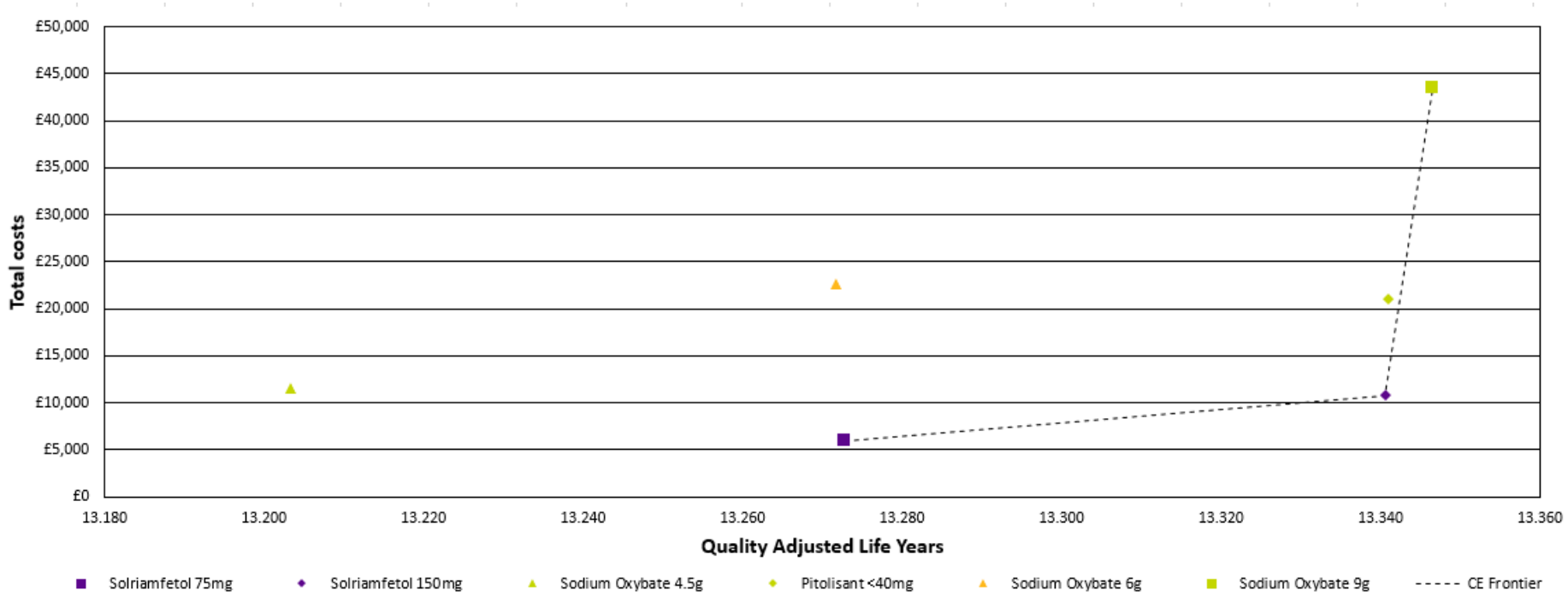
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. * South-West Quadrant of cost-effectiveness plane

Table 49. Base-case results – Combined

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

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

Figure 20. Cost-effectiveness plane for base case results



Abbreviations: CE, cost-effectiveness.

To facilitate comparisons with some of the scenario analysis the results generated using the raw IPD solriamfetol 150 mg data and the associated pseudo-IPD for the comparators are presented in Table 50 and Table 51

Table 50. Base-case results: Live data – By dose

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

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

Table 51. Base-case results: Live data – Combined

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

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

The results are highly congruent and reinforce the results from the bootstrapped analysis demonstrating that in both the individual dose analysis and the combined analysis solriamfetol is the cost-effective treatment of choice.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

PSA tests the impact of second order uncertainty by random, simultaneous variation of the input parameters on the model. Second order uncertainty does not include cohort characteristics, which are part of first order uncertainty. To account for this the model used the bootstrapping methods previously described (see Section B.3.3.1) to generate a cohort of 5,000 patients from the IPD for each subsequent draw of input parameters. By using the IPD to sample patients, the associated uncertainty with regards to patient age and the proportion of female patients was automatically captured and was therefore not included as a specific parameter in the PSA.

PSA analysis was performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions to estimate the cost-effectiveness ratios. A normal distribution was applied to the mean change in ESS relative to solriamfetol 150 mg for all comparators. A Beta distribution was assigned to probabilities, proportions, and data which are limited to values between 0 and 1. A Gamma distribution was assigned to costs, doses, and resource use, which take positive values and were likely to be positively skewed. The Alpha and Beta values of the distribution were estimated based on the mean and SD associated with each parameter.

If the SD was not available from the reporting study, it was calculated based on the following assumption:

= (Upper range – lower range)/(2*NORMSINV(0.975))

The upper and lower ranges were based on CIs/CrIs where reported, or where not reported, were based on a variation of +/- 20%.

Due to the use of the IPD, bootstrapping methods were implanted to capture the uncertainty with regards to baseline ESS, change in ESS from baseline, age and gender split within the data (156). A total of 10,000 Monte Carlo simulations were recorded, the results were plotted on the cost-effectiveness plane (CEP), and a cost-effectiveness acceptability curve (CEAC) was generated. The CEP showed the

distribution of incremental cost and benefits under uncertainty and the CEAC showed the likelihood of being cost-effective at given acceptability thresholds.

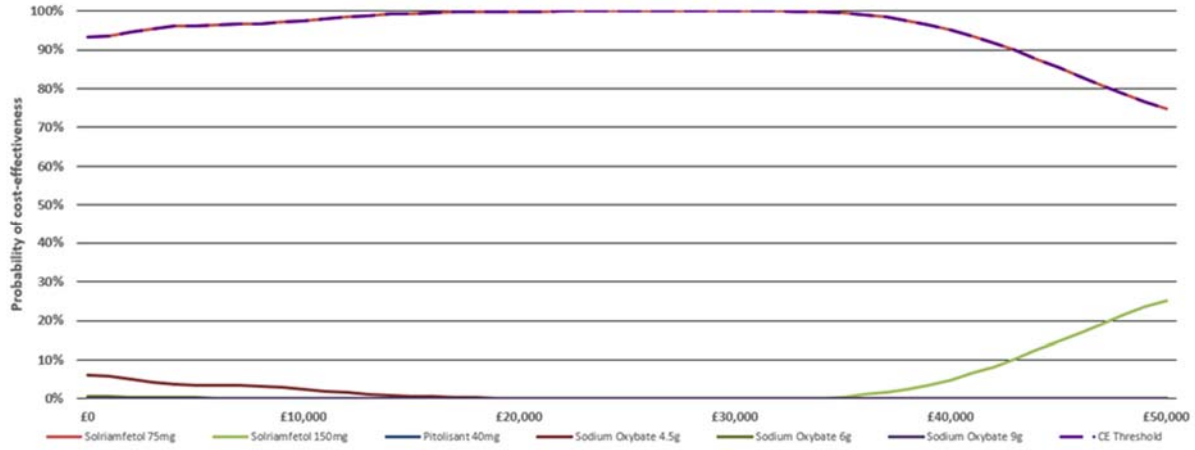
The probability that solriamfetol 75 mg was the most cost-effective treatment at a threshold of £20,000 per QALY was 99.87% and 0.00% with the 150 mg formulation (Figure 21) giving a combined probability of 99.87% that solriamfetol would be cost effective at a willingness to pay threshold of £20,000 per QALY, this increases to 99.98% and 0.01% for the 75 mg and 150 mg formulations respectively, at a threshold of £30,000 per QALY, giving a combined probability of 99.99% that solriamfetol would be cost-effective. Across 10,000 PSA simulations, solriamfetol 75 mg was associated with a mean cost of £5,314 (95% CI: £5,299, £5,329) and a mean total QALYs of 13.166 (95% CI: 13.151, 13.180) whilst solriamfetol 150 mg was associated with a mean cost of £10,813 (95% CI: £10,801, 10,824) and a mean total QALYs of 13,258 (95% CI: 13.244, 13.272) (Table 52). These results are highly congruent with the deterministic results. The PSA results in a slight shift in the position of pitolisant in the full incremental analysis, dropping it between sodium oxybate 6g and 9g, but pitolisant remains extendedly dominated versus solriamfetol 75 mg. Overall the results remain consistent with the base case analysis with the solriamfetol doses demonstrating dominance or high cost-effectiveness over all other treatments considered in the analysis.

Table 52. Probabilistic sensitivity analysis results

Technologies	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£5,314 (£5,299 - £5,329)	13.166 (13.151 - 13.180)				
Solriamfetol 150mg	£10,813 (£10,801 - £10,824)	13.258 (13.244 - 13.272)	£5,498	0.092	£59,464	£59,464
Sodium Oxybate 4.5g	£11,042 (£11,019 - £11,066)	13.111 (13.097 - 13.126)	£230	-0.147	Dominated	Dominated
Sodium Oxybate 6g	£19,305 (£19,208 - £19,403)	13.158 (13.145 - 13.171)	£8,263	0.047	£176,319	Dominated
Pitolisant <40mg	£20,377 (£20,374 - £20,380)	13.250 (13.237 - 13.263)	£1,072	0.092	£11,659	Extendedly dominated
Sodium Oxybate 9g	£45,469 (£45,434 - £45,505)	13.275 (13.261 - 13.289)	£25,093	0.025	£1,003,445	£367,490

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Figure 21. Cost-effectiveness acceptability curve



Abbreviations: CE, cost-effectiveness.

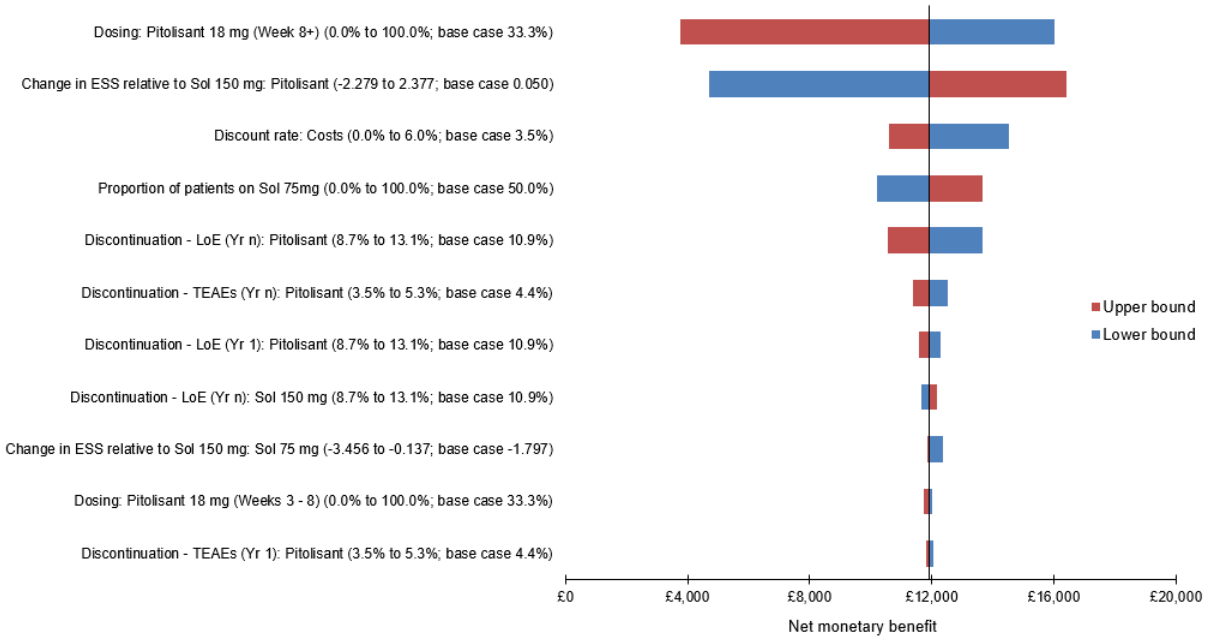
B.3.8.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis in which all model variables were systematically and independently varied over a plausible range determined by either the 95% CI, or +/- 20% where no estimates of precision were available. Because solriamfetol dominates sodium oxybate or results in high ICERs

within the South-West quadrant of the cost-effectiveness plane, the univariate analysis was based on the net monetary benefit (NMB), assuming a willingness to pay threshold of £20,000 per QALY, was assessed instead of the ICER, a scenario analysis considering a willingness to pay threshold of £30,000 per QALY is presented in Appendix J. In this analysis a positive NMB favours solriamfetol. The NMB was recorded at the upper and lower values for each parameter to produce a tornado diagram. To avoid the introduction of unnecessary uncertainty, the univariate analysis was based on the raw IPD and the associated pseudo-IPD dataset. The bootstrapped results were congruent with those produced using the raw IPD and the analysis based on the raw IPD identified the key drivers within the analysis. In addition, the results presented were based on the combined analysis although all individual dose parameters were varied independently.

Figure 22 presents the results of the univariate sensitivity analysis for solriamfetol versus pitolisant in the form of a tornado diagram. Note that all parameters were varied (see Table 46) but the tornado diagrams show the 10 parameters with the greatest impact. These results are also presented in Table 53. The most influential parameters included: the proportion of patients on the 18mg dose of pitolisant beyond 8 weeks, the rate of discontinuation for all treatments due to loss of efficacy or AEs, and the changes in ESS relative to solriamfetol 150 mg. Importantly, no parameter tested in univariate sensitivity, and the scenario presented in Appendix J, resulted in a negative NMB for solriamfetol, further demonstrating the robustness of the base case result.

Figure 22. Results of univariate analysis: solriamfetol vs pitolisant (tornado diagram)



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.

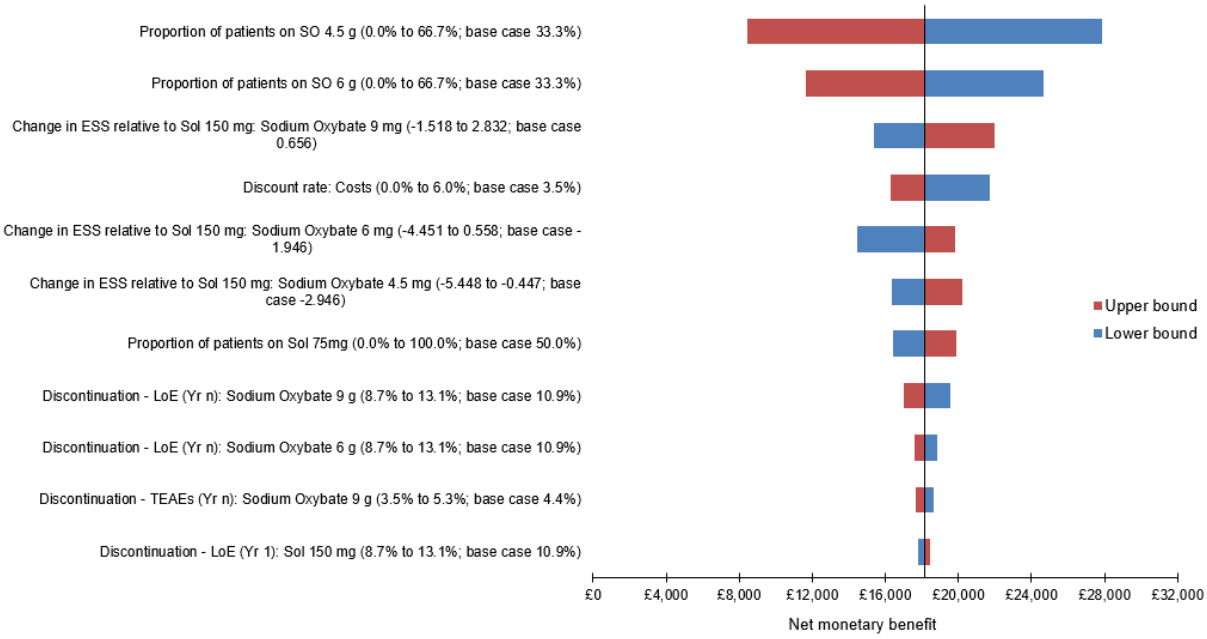
Table 53. Results of univariate analysis: solriamfetol vs pitolisant

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 75mg (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.

Figure 23 presents the results of the univariate sensitivity analysis for solriamfetol versus sodium oxybate in the form of a tornado diagram. Note that all parameters were varied but Figure 23 shows the 10 parameters with the greatest impact. These results are also presented in Table 54. The most influential parameters included the proportion of patients on each dose of sodium oxybate, the change in ESS for each sodium oxybate dose relative to solriamfetol 150mg and rates of discontinuation. As with the comparison to pitolisant, no parameter tested in resulted in an NMB below zero, further demonstrating the robustness of the base case result.

Figure 23. Results of univariate analysis: solriamfetol vs sodium oxybate



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 54. 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 SO 4.5 g (0.0% to 66.7%; base case 33.3%)	£27,880	£8,414
Proportion of patients on SO 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
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 75mg (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

B.3.8.3 Threshold analysis

Threshold analysis was performed on the top 10 model parameters (as identified in the univariate sensitivity analysis above) to determine at which values solriamfetol would no longer result in a positive NMB at a willingness to pay threshold of £20,000 per QALY. In this analysis, all other parameters were kept at their original value. As with the univariate analysis the threshold analysis was performed on the raw IPD. Results of the threshold analysis are presented in Table 55 which compares solriamfetol to sodium oxybate and Table 56 which compares solriamfetol to pitolisant, a scenario analysis using a willingness to pay threshold of £30,000 per QALY is presented in Appendix J.

Table 55. Results of threshold analysis: solriamfetol versus sodium oxybate

Variable	Base case (Lower bound to Upper bound)	Value to achieve £0 net monetary benefit
Proportion of patients on SO 4.5 g	33.3% (0.0% to 66.7%)	95.5%*
Proportion of patients on SO 6 g	33.3% (0.0% to 66.7%)	126.6%*
Change in ESS relative to Sol 150 mg: Sodium Oxybate 9 g	0.656 (-1.518 to 2.832)	NA
Discount rate: Costs	3.5% (0.0% to 6.0%)	NA
Change in ESS relative to Sol 150 mg: Sodium Oxybate 6 g	-1.946 (-4.451 to 0.558)	NA
Change in ESS relative to Sol 150 mg: Sodium Oxybate 4.5 g	-2.946 (-5.448 to -0.447)	NA
Proportion of patients on Sol 75mg	50.0% (0.0% to 100.0%)	-478.1%*
Discontinuation - LoE (Yr n): Sodium Oxybate 9 g	10.9% (8.7% to 13.1%)	NA
Discontinuation - LoE (Yr n): Sodium Oxybate 6 g	10.9% (8.7% to 13.1%)	NA
Discontinuation - TEAEs (Yr n): Sodium Oxybate 9 g	4.4% (3.5% to 5.3%)	NA

Abbreviations: ICER, incremental cost-effectiveness ratio; LoE, loss of efficacy; NA, not applicable (No value could be determined); QALYs, quality-adjusted life years; TEAEs, treatment emergent adverse events; Yr 1, Year one; Yr n, Years 2 and beyond. * Outside of a plausible range.

Table 56. Results of threshold analysis: solriamfetol versus pitolisant

Variable	Base case (Lower bound to Upper bound)	Value to achieve £0 net monetary benefit
Dosing: Pitolisant 18 mg (Week 8+)	33.3% (0.0% to 100.0%)	130.9%*
Change in ESS relative to Sol 150 mg: Pitolisant	0.050 (-2.279 to 2.377)	NA
Discount rate: Costs	3.5% (0.0% to 6.0%)	NA
Proportion of patients on Sol 75mg	50.0% (0.0% to 100.0%)	-297.3%*
Discontinuation - LoE (Yr n): Pitolisant	10.9% (8.7% to 13.1%)	142.1%*
Discontinuation - TEAEs (Yr n): Pitolisant	4.4% (3.5% to 5.3%)	147.0%*
Discontinuation - LoE (Yr 1): Pitolisant	10.9% (8.7% to 13.1%)	88.5%*
Discontinuation - LoE (Yr n): Sol 150 mg	10.9% (8.7% to 13.1%)	-7.3%*
Change in ESS relative to Sol 150 mg: Sol 75 mg	-1.797 (-3.456 to -0.137)	NA
Dosing: Pitolisant 18 mg (Weeks 3 - 8)	33.3% (0.0% to 100.0%)	4,157.9%*

Abbreviations: ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio; LoE, loss of efficacy; NA, not applicable (No value could be determined); QALY, quality-adjusted life year; TEAEs, treatment emergent adverse events. Yr 1, Year one; Yr n, Years 2 and beyond * Outside of a plausible range.

In both sets of analysis when parameters were considered individually, and all other parameters remained unchanged, no plausible values could be identified that would result in negative NMB for solriamfetol. Note that, the Excel Goal Seek functionality

used to perform the threshold analysis can generate illogical answers, although mathematically correct, for example; when comparing solriamfetol to sodium oxybate a zero NMB can be achieved if the proportion of patients on sodium oxybate 4.5 g is greater than 95.5%. In this scenario, the proportion on patients on 6 g is set to 33.3% and the total of those on 4.5 g, 6 g and 9 g must total 100% resulting in a negative figure for 9 g. All such illogical outcomes have been indicated in the respective tables.

B.3.8.4 Scenario analysis

Alternative time point assessment of response

As discussed in Section B.3.7, the base case analysis assumed that the clinical assessment of response was conducted at week 8 to reflect the majority of the data identified for the comparators.

The primary end-point for TONES 2 was at 12 weeks thus a scenario analysis using the primary end-point ITC (Section B.2.9.2.5) is considered. This analysis utilised the 12 week IPD for solriamfetol 150 mg TONES 2 and applied the mean change in ESS relative to solriamfetol 150 mg for each treatment to generate an alternative pseudo-IPD dataset. Table 57 presents the mean change in ESS relative to solriamfetol and the associated absolute ESS scores for responders and non-responders at week 12. By extending the analysis to the 12-week primary end-point of TONES 2, solriamfetol 150 mg has a greater reduction in ESS than all of the comparators.

Table 57. Primary end-point analysis – 12-week end-point

Product, daily dose	Mean ΔESS relative to solriamfetol 150 mg at week 12 (95% CrI)a	Absolute ΔESS from baseline[b] (all patients†)	Proportion of responders (ΔESS from baseline ≥3)	Mean ESS in responders at week 12	Mean ESS in non-responders at week 12
Solriamfetol, 75 mg	−1.596 (−3.437, 0.242)*	-3.74	46%	8.37	17.76
Solriamfetol, 150 mg	Reference product	-5.33‡	63%	8.65	17.04
Pitolisant (≤40 mg)	-0.656 (−3.107,1.788)	-4.68	50%	7.90	16.98
Sodium oxybate, 4.5 g	-3.646 (−6.276, −1.017)*	-1.69	30%	9.74	19.21
Sodium oxybate, 6.0 g	−2.647 (−5.276, -0.023)	-2.69	41%	9.38	18.61
Sodium oxybate, 9.0 g	-0.044 (−2.347, 2.262)	-5.29	50%	7.28	16.39

Abbreviations: CrI, credible interval; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness scale; IPD, individual patient data.
Δ represents change in ESS from baseline.
* Change compared to solriamfetol 150 mg (CrI did not cross 0).
† All patients, irrespective of response/non-response; ‡Change estimated via IPD.
a. With regards to the mean change in ESS relative to solriamfetol 150mg; a negative figure means that the comparator is less effective than solriamfetol 150mg with comparative efficacy reducing as this figure moves further from zero. Conversely, a positive figure means that the comparator is more effective than solriamfetol 150 mg with the comparative efficacy increasing as the figure moves further from zero.
b. With regards to the absolute change in ESS from baseline; Patients with EDS will have a high ESS as symptoms improve the ESS will reduce, as such a negative figure demonstrates the improvement in a patient's symptoms. As the figure moves further from zero the less EDS a patient will experience.

The results presented in Table 58 and Table 59 demonstrate that using the primary end-point analysis are again congruent with the base case analysis and solriamfetol is cost-effective compared to both pitolisant and sodium oxybate. However, in this primary end-point scenario, both doses of solriamfetol form the cost-effectiveness frontier (Figure 24) meaning that pitolisant and sodium oxybate are either dominated or extendedly dominated by the two formulation of solriamfetol

Figure 24. Cost-effectiveness plane for primary end-point analysis

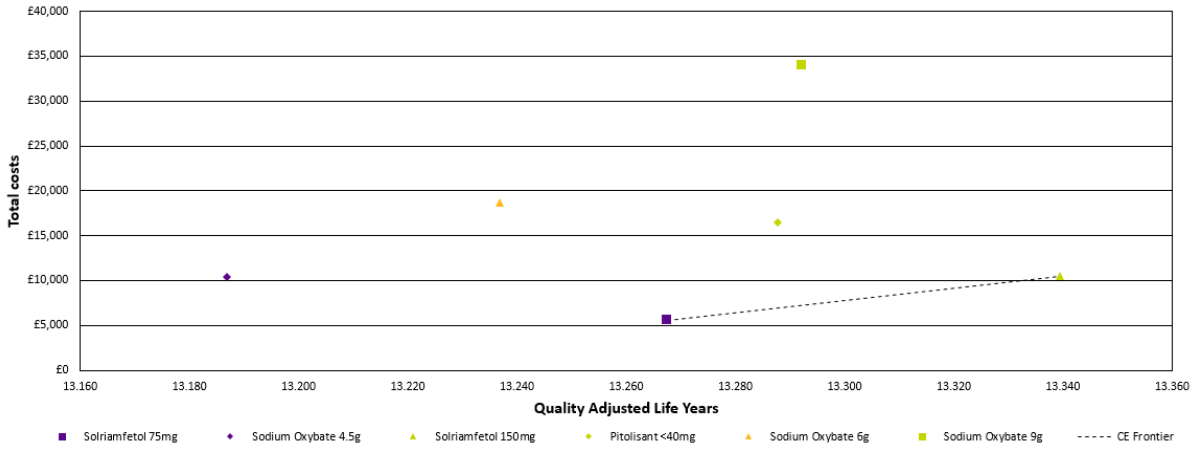


Table 58. Scenario analysis: Assessment of response at 12 weeks – By dose

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£5,591 (£5,589 - £5,593)	13.268 (13.265 - 13.270)	42.039 (42.021 - 42.058)				
Sodium Oxybate 4.5g	£10,429 (£10,418 - £10,439)	13.187 (13.184 - 13.190)	42.039 (42.021 - 42.058)	£4,838	-0.081	Dominated	Dominated
Solriamfetol 150mg	£10,512 (£10,512 - £10,512)	13.339 (13.336 - 13.342)	42.039 (42.021 - 42.058)	£83	0.153	£546	£68,490
Pitolisant <40mg	£16,446 (£16,443 - £16,449)	13.288 (13.285 - 13.291)	42.039 (42.021 - 42.058)	£5,934	-0.052	Dominated	Extendedly dominated
Sodium Oxybate 6g	£18,719 (£18,717 - £18,720)	13.237 (13.234 - 13.240)	42.039 (42.021 - 42.058)	£2,273	-0.051	Dominated	Dominated
Sodium Oxybate 9g	£34,030 (£34,023 - £34,037)	13.292 (13.289 - 13.295)	42.039 (42.021 - 42.058)	£15,312	0.056	£275,857	Extendedly dominated

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

Table 59. Scenario analysis: Assessment of response at 12 weeks – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,052	13.303	42.039			
Pitolisant	£16,446	13.288	42.039	£8,394	-0.016	Dominated
Sodium oxybate	£21,059	13.239	42.039	£4,613	-0.049	Dominated

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

Alternative model time horizon

The base case analysis assumes a lifetime horizon as narcolepsy is a chronic condition. Previous analysis, such as that conducted by Lanting 2014 (133) have considered shorter time horizons. For completeness a scenario analysis considering alternative time horizons is presented in Table 63. This analysis demonstrates solriamfetol remains cost-effective compared to pitolisant and dominant when compared to sodium oxybate at all time horizons considered.

Table 60. Scenario analysis: Alternative model time horizon

Model time horizon (years)	ICER for solriamfetol vs. Pitolisant	ICER for solriamfetol vs. Sodium oxybate
5	£369,432.64	Dominant
10	£367,902.81	Dominant
15	£367,544.74	Dominant
20	£367,429.85	Dominant
25	£367,389.79	Dominant
30	£367,375.61	Dominant
35	£367,370.68	Dominant
40	£367,369.02	Dominant
45	£367,368.52	Dominant
50	£367,368.38	Dominant
55	£367,368.36	Dominant
60	£367,368.36	Dominant
65	£367,368.35	Dominant
70	£367,368.35	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio

Alternative definition of response

The literature supports a reduction in ESS of between 2–4 as being a clinically relevant change (90-92), and based on KOL feedback there is variability in the absolute use of ESS in clinical practice (and there is no officially recognised definition of

response based on reduction in ESS)(2). It was therefore reasonable that the base case analysis (using a midpoint) assumed that 'response' was a reduction in ESS ≥3 points (60). However, scenarios are then included using an ESS reduction of ≥2 as presented in Table 61, and Table 62**,** and scenarios using an ESS reduction of ≥4 are presented in Table 63 and Table 64.

Table 61. Scenario analysis: Response is a reduction in ESS ≥2 – Separate doses

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£6,828 (£6,825 - £6,831)	13.298 (13.294 - 13.302)	42.040 (42.017 - 42.063)				
Solriamfetol 150mg	£12,261 (£12,259 - £12,263)	13.372 (13.368 - 13.376)	42.040 (42.017 - 42.063)	£5,433	0.074	£73,372	£73,372
Sodium Oxybate 4.5g	£15,716 (£15,714 - £15,718)	13.235 (13.231 - 13.239)	42.040 (42.017 - 42.063)	£3,455	-0.137	Dominated	Dominated
Pitolisant <40mg	£23,889 (£23,886 - £23,893)	13.372 (13.368 - 13.376)	42.040 (42.017 - 42.063)	£8,173	0.137	£59,460	Extendedly dominated
Sodium Oxybate 6g	£25,812 (£25,800 - £25,824)	13.296 (13.292 - 13.300)	42.040 (42.017 - 42.063)	£1,923	-0.076	Dominated	Dominated
Sodium Oxybate 9g	£49,592 (£49,586 - £49,599)	13.379 (13.375 - 13.383)	42.040 (42.017 - 42.063)	£23,780	0.083	£288,131	£529,706

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

Table 62. Scenario analysis: Response is a reduction in ESS ≥2 – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£9,545	13.335	42.040			
Pitolisant	£23,889	13.372	42.040	£14,345	0.038	£382,187
Sodium oxybate	£30,373	13.303	42.040	£6,484	-0.069	Dominated

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

Table 63. Scenario analysis: Response is a reduction in ESS ≥4 – Separate doses

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£4,468 (£4,464 - £4,473)	13.228 (13.226 - 13.230)	42.055 (42.039 - 42.072)				
Sodium Oxybate 4.5g	£9,647 (£9,638 - £9,656)	13.186 (13.184 - 13.187)	42.055 (42.039 - 42.072)	£5,178	-0.042	Dominated	Dominated
Solriamfetol 150mg	£9,858 (£9,855 - £9,860)	13.323 (13.321 - 13.325)	42.055 (42.039 - 42.072)	£211	0.137	£1,539	£56,821
Sodium Oxybate 6g	£16,885 (£16,870 - £16,901)	13.227 (13.225 - 13.229)	42.055 (42.039 - 42.072)	£7,028	-0.096	Dominated	Dominated
Pitolisant <40mg	£19,229 (£19,225 - £19,234)	13.323 (13.321 - 13.325)	42.055 (42.039 - 42.072)	£2,344	0.096	£24,394	Extendedly dominated
Sodium Oxybate 9g	£39,849 (£39,840 - £39,859)	13.328 (13.326 - 13.330)	42.055 (42.039 - 42.072)	£20,620	0.005	£4,074,177	£352,670

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

Table 64. Scenario analysis: Response is a reduction in ESS ≥4 – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£7,163	13.275	42.055			
Pitolisant	£19,229	13.323	42.055	£12,066	0.048	£252,222
Sodium oxybate	£22,127	13.247	42.055	£2,898	-0.076	Dominated

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

Alternative discontinuation rates

The current base case analysis assumes that discontinuation can occur due to a lack of efficacy (10.9% per annum), or due to AEs (4.4% per annum). This is based on a limited data set for solriamfetol, the one-year data from TONES 5, and an assumption that the rates of discontinuation for the comparators are equal to those for solriamfetol. Therefore, the following analyses consider a series of hypothetical scenarios where:

- Discontinuation rates for the comparators, from year two onwards, are set to half the current value
- Discontinuation rates for the comparators, from year two onwards, are set to zero
- Discontinuation rates for the comparators, from year two onwards, are set to twice the current value

Table 65. Discontinuation rates for the comparators, from year two onwards, are set to half the current value

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,370	13.369	42.445			
Pitolisant	£32,694	13.559	42.445	£24,324	0.190	£127,706
Sodium oxybate	£40,305	13.454	42.445	£7,612	-0.105	Dominated

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

Table 66. Discontinuation rates for the comparators, from year two onwards, are set to zero

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,370	13.369	42.445			
Pitolisant	£75,098	14.125	42.445	£66,728	0.756	£88,248
Sodium oxybate	£92,646	13.883	42.445	£17,548	-0.242	Dominated

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

Table 67. Discontinuation rates for the comparators, from year two onwards, are set to twice the current value

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,370	13.369	42.445			
Pitolisant	£13,020	13.297	42.445	£4,650	-0.072	Dominated
Sodium oxybate	£16,022	13.255	42.445	£3,002	-0.041	Dominated

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

In the conservative scenarios, with reduced discontinuation for pitolisant and sodium oxybate, the costs for each treatment increase, as more patients remained on treatment and the QALYs also increase accordingly. However, these changes still result in solriamfetol dominating sodium oxybate and the ICER for Pitolisant exceeding traditionally accepted thresholds. In the alternative scenario where discontinuation increases with the comparators solriamfetol dominates both pitolisant and sodium oxybate. In all three scenarios solriamfetol remains cost-effective versus both pitolisant and sodium oxybate.

Alternative solriamfetol market share

The current combined base case analysis assumes a 50/50 split of solriamfetol 75 mg and 150 mg based on current real-world usage in the US. Illustrative alternative scenarios using a 30/70 and 70/30 split for solriamfetol 75 mg and 150 mg are presented in Table 68 and Table 69.

Table 68. Alternative solriamfetol market split – 30% on 75 mg and 70% on 150mg

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£9,328	13.382	42.445			
Pitolisant	£20,991	13.403	42.445	£11,662	0.021	£560,858
Sodium oxybate	£25,860	13.336	42.445	£4,870	-0.037	Dominated

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

Table 69. Alternative solriamfetol market split – 70% on 75 mg and 30% on 150mg

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£7,411	13.355	42.445			
Pitolisant	£20,991	13.403	42.445	£13,579	0.048	£283,401
Sodium oxybate	£25,860	13.336	42.445	£4,870	-0.067	Dominated

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

As both formulations of solriamfetol are on the cost-effectiveness frontier the change in market share has no impact on the overall conclusion of the analysis (See Table 68 and Table 69) with solriamfetol remaining the most cost-effective treatment choice.

Alternative HRQoL estimates

A range of alternative data sources for linking ESS to QoL were assessed, and the following section considers the various data sources identified and the impact that they had on the cost-effectiveness outcomes.

OSA based QoL estimates from McDaid

McDaid 2007 (139) used the surrogate end point of ESS score as a proxy for differences in utility. McDaid 2007 used three sets of IPD (two measuring ESS and SF-36 profile in the same patients; one measuring ESS, SF-36 profile and EQ-5D-3L in the same set of patients) to map ESS scores to EQ-5D-3L and 6-Dimension Short Form 36 Health Survey (SF-6D) values (based on tariffs published by Brazier 2002 (172) and Dolan 1995 (173)) using linear regression analyses. The results of this process indicated that a unit fall in ESS score for patient with OSA is associated with an increase in utility, based on a SF-6D (n=294) value of 0.0095 (95% CI 0.0070 to 0.0123) and based on an EQ-5D-3L (n=94) value of 0.0097 (95% CI 0.0019 to 0.0175). Lanting 2014 (133) made the assertion that the relationship between ESS score and utility change was not disease specific and assumed the relationship between ESS change and utility change would be similar for patients with narcolepsy. Therefore a scenario analysis that utilised the ESS to EQ-5D regression analysis from McDaid 2007 is presented in Table 70 and Table 71.

Table 70. Scenario analysis: ESS to EQ-5D McDaid 2007 regression – By dose

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£5,974 (£5,972 - £5,977)	16.825 (16.821 - 16.828)	42.041 (42.023 - 42.059)				
Solriamfetol 150mg	£10,764 (£10,756 - £10,773)	16.896 (16.892 - 16.899)	42.041 (42.023 - 42.059)	£4,790	0.071	£67,224	£67,224
Sodium Oxybate 4.5g	£11,467 (£11,464 - £11,471)	16.769 (16.766 - 16.772)	42.041 (42.023 - 42.059)	£703	-0.127	Dominated	Dominated
Pitolisant <40mg	£20,987 (£20,970 - £21,003)	16.897 (16.894 - 16.901)	42.041 (42.023 - 42.059)	£9,520	0.129	£74,073	Extendedly dominated
Sodium Oxybate 6g	£22,582 (£22,572 - £22,592)	16.821 (16.817 - 16.824)	42.041 (42.023 - 42.059)	£1,595	-0.077	Dominated	Dominated
Sodium Oxybate 9g	£43,524 (£43,489 - £43,558)	16.917 (16.914 - 16.921)	42.041 (42.023 - 42.059)	£20,942	0.096	£217,764	£406,228

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

Table 71. Scenario analysis: ESS to EQ-5D McDaid 2007 regression - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,369	16.860	42.041			
Pitolisant	£20,987	16.897	42.041	£12,618	0.037	£338,817
Sodium oxybate	£25,858	16.836	42.041	£4,871	-0.062	Dominated

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

All scenarios were based on a bootstrapped analysis which resulted in nominal variation in the total costs and while there was some variation in the absolute QALYs achieved with each treatment, as to be expected with the alternative regressions, the relative changes in incremental QALYs were not impacted significantly. Again, this is unsurprising because the regressions were applied to all treatments. The results between the two scenarios are very similar due to the similarities between the coefficients of the respective regressions. As a consequence, the ICERs and

conclusions were congruent with the base case analysis and solriamfetol remained the cost-effective treatment of choice.

Alternative approach to pseudo-IPD generation

The current base case analysis assumes that the change in ESS for each comparator, relative to solriamfetol 150 mg, is applied to the IPD equally. That is to say, the change in ESS from baseline is the same irrespective of the base line ESS for the solriamfetol 150 mg IPD. As noted in Section B.3.3.1, there is no data available to inform any potential skew in the data, such that patients with higher/lower baseline ESS scores may be affected differently, and this was noted as a potential limitation to the analysis. To address this limitation a scenario analysis has been conducted to skew the change in ESS for the comparators relative to solriamfetol 150 mg. To conduct this analysis, we have assumed that the mean change in ESS for each comparator is fixed to the mean baseline ESS score for the population (ESS=17). We have then assumed that the baseline ESS could range from 10-24 and estimated the difference relative to solriamfetol 150 mg at each alternative baseline ESS, assuming a linear distribution, such that the mean change across all potential baseline ESS scores remains constant but that the distribution is skewed to the left, the comparator will perform better at lower baseline ESS scores, or to the right, the comparator will perform better at higher baseline ESS scores.

Table 72. Scenario analysis: Pseudo-IPD skewed low (to the left)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,370	13.369	42.445			
Pitolisant	£23,905	13.428	42.445	£15,535	0.059	£264,158
Sodium oxybate	£28,298	13.302	42.445	£4,393	-0.125	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 73. Scenario analysis: Pseudo-IPD skewed high (to the right)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,370	13.369	42.445			
Pitolisant	£23,905	13.430	42.445	£15,535	0.061	£253,940

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Sodium oxybate	£29,719	13.311	42.445	£5,814	-0.119	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Both scenarios presented in Table 72 and Table 73 demonstrate that the skew has no impact on the conclusion of the analysis that solriamfetol remains the cost-effective treatment compared to pitolisant and sodium oxybate.

Other comparators

As previously discussed, the evidence required to perform a robust and meaningful comparison with methylphenidate and dexamfetamine was not available following both an initial SLR, and a subsequent widened search that allowed data of lower quality to be included. This prevented the inclusion of these comparators in a robust network meta-analysis, and as such, in the base case analysis, these treatments were not considered. In order to provide some level of comparison with these comparators (as defined in the company submission problem, Table 1) a scenario analysis was conducted that modelled hypothetical changes in ESS relative to solriamfetol 150mg.

To conduct this scenario analysis, a hypothetical two-way sensitivity analysis was conducted for each of dexamphetamine and methylphenidate MR that considered both a variable change in ESS relative to solriamfetol 150 mg in increments of one, and a range of doses within the credible ranges for each product (dexamfetamine and methylphenidate). The model used the Excel Data table functionality which required the calculations to be 'live', thus the analysis was based on the raw IPD and the associated pseudo-data generated for the comparator. For simplicity, the analysis is presented against the weighted solriamfetol costs and QALYs. The substantial limitations of this analysis due to the absence of comparative data and the impact of this on the conclusions that can be drawn from this analysis should be acknowledged.

Dexamfetamine

Dexamfetamine is available as a tablet and as an oral solution (rarely used) with multiple strengths available (63, 64). The recommended starting dose of dexamfetamine is 10 mg per day, given in divided doses. Dosage may be increased if necessary, by 10 mg per day at weekly intervals to a suggested maximum of 60 mg per day. This analysis assumes that a split dose of dexamfetamine would be taken daily, with the lowest cost tablet combination used, and explores a range of efficacy values assuming that the change in ESS relative to solriamfetol 150 mg ranges from -1 to -7 (i.e. dexamfetamine is assumed to be less effective than solriamfetol 150 mg in each of the scenarios).

Table 74. Drug acquisition costs: Dexamfetamine

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

Source: National Drug Tariff (154).
* Oral solution available but clinicians advised that it is rarely used.

Table 75. Scenario analysis: solriamfetol 75 mg vs dexamfetamine tablets

		Dose of dexamfetamine					
Formulation		**10mg**	**20mg**	**30mg**	**40mg**	**50mg**	**60mg**
Price per day		**£1.65**	**£2.65**	**£4.30**	**£5.30**	**£6.95**	**£7.96**
ΔESS relative to solriamfetol 150 mg at week 8	-1.00	Dominated	Dominated	Dominated	Dominated	£44,523	£72,905*
	-2.00	£3,043,324	£2,391,430	£1,323,673	£671,779	Dominant	Dominant
	-3.00	£70,575	£61,392	£46,351	£37,168	£22,126	£12,943
	-4.00	£47,183	£42,916	£35,927	£31,661	£24,672	£20,405
	-5.00	£39,797	£37,067	£32,595	£29,865	£25,393	£22,663
	-6.00	£32,129	£30,795	£28,609	£27,275	£25,089	£23,755
	-7.00	£29,693	£28,839	£27,438	£26,584	£25,183	£24,329

* South-west quadrant of the cost-effectiveness plane (solriamfetol is less costly and less effective).

Table 76. Scenario analysis: solriamfetol 150 mg vs. dexamfetamine tablets

	Dose of dexamfetamine					
	10mg	**20mg**	**30mg**	**40mg**	**50mg**	**60mg**

ΔESS relative to solriamfetol 150 mg at week 8	-1.00	£313,806	£274,576	£210,321	£171,091	£106,835	£67,606
	-2.00	£133,002	£119,335	£96,950	£83,283	£60,897	£47,230
	-3.00	£70,627	£65,971	£58,345	£53,689	£46,062	£41,406
	-4.00	£56,132	£53,490	£49,163	£46,521	£42,194	£39,552
	-5.00	£50,127	£48,310	£45,334	£43,518	£40,542	£38,725
	-6.00	£42,937	£41,976	£40,404	£39,443	£37,871	£36,911
	-7.00	£40,386	£39,755	£38,720	£38,088	£37,053	£36,421

* South-west quadrant of the cost-effectiveness plane (solriamfetol is less costly and less effective).

Table 77. Scenario analysis: solriamfetol vs. dexamfetamine tablets

		Dose of dexamfetamine					
		10mg	**20mg**	**30mg**	**40mg**	**50mg**	**60mg**
ΔESS relative to solriamfetol 150 mg at week 8	-1.00	Dominated	Dominated	Dominated	Dominated	Dominated	£86,771
	-2.00	£192,764	£165,992	£122,140	£95,367	£51,515	£24,743
	-3.00	£70,610	£64,430	£54,309	£48,130	£38,009	£31,830
	-4.00	£52,710	£49,446	£44,102	£40,839	£35,494	£32,231
	-5.00	£45,999	£43,818	£40,244	£38,062	£34,489	£32,307
	-6.00	£38,414	£37,297	£35,468	£34,351	£32,522	£31,405
	-7.00	£35,842	£35,115	£33,925	£33,199	£32,009	£31,282

* South-west quadrant of the cost-effectiveness plane (solriamfetol is less costly and less effective)

Methylphenidate (unlicensed in narcolepsy)

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. Methylphenidate is available as either an IR or MR tablet with multiple strengths and formulations available. KOL Clinical Practice Interviews indicated widespread use of and preference for, methylphenidate MR in narcolepsy. Based on this feedback, IR preparations have been excluded.

In the case of methylphenidate, which is unlicensed for the treatment of narcolepsy, dosage recommendations from the EFNS guidelines on narcolepsy have been applied (11). The BNF states that “Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of methylphenidate, prescribers should specify the brand to be dispensed” (178). The KOL Clinical Practice Interviews indicated widespread

use of and preference for, methylphenidate MR in narcolepsy (2). Based on this feedback, IR preparations have been excluded and the branded MR products have been used. This analysis assumes that a single tablet would be taken daily and explores a range of efficacy values assuming that the change in ESS relative to solriamfetol 150 mg ranges from -1 to -7 (i.e. methylphenidate is assumed to be less effective than solriamfetol 150 mg in each of the scenarios).

Table 78. Drug acquisition costs: Methylphenidate

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

Table 79. Scenario analysis: solriamfetol 75 mg vs. methylphenidate MR tablets

		Dose of methylphenidate				
Dose		**18mg**	**27mg**	**36mg**	**54mg**	**72mg**
Cost per day		**£1.04**	**£1.23**	**£1.42**	**£1.23**	**£2.84**
ΔESS relative to solriamfetol 150 mg at week 8	-1.00	Dominated	Dominated	Dominated	Dominated	Dominated
	-2.00	£3,436,709	£3,313,506	£3,190,303	£3,313,506	£2,269,525
	-3.00	£76,117	£74,381	£72,646	£74,381	£59,675
	-4.00	£49,757	£48,951	£48,145	£48,951	£42,118
	-5.00	£41,444	£40,928	£40,412	£40,928	£36,556
	-6.00	£32,934	£32,682	£32,430	£32,682	£30,545
	-7.00	£30,209	£30,048	£29,886	£30,048	£28,679

Table 80. Scenario analysis: solriamfetol 150 mg vs. methylphenidate MR tablets

		Dose of methylphenidate				
Dose		**18mg**	**27mg**	**36mg**	**54mg**	**72mg**
Cost per day		**£1.04**	**£1.23**	**£1.42**	**£1.23**	**£2.84**
ΔESS relative to solriamfetol 150 mg at	-1.00	£337,479	£330,065	£322,651	£330,065	£267,240
	-2.00	£141,250	£138,667	£136,084	£138,667	£116,779
	-3.00	£73,437	£72,557	£71,677	£72,557	£65,100
	-4.00	£57,726	£57,227	£56,727	£57,227	£52,996
	-5.00	£51,224	£50,880	£50,537	£50,880	£47,971
	-6.00	£43,516	£43,335	£43,153	£43,335	£41,797
	-7.00	£40,768	£40,648	£40,529	£40,648	£39,636

Table 81. Scenario analysis: solriamfetol versus methylphenidate MR tablets

		Dose of methylphenidate				
		18mg	**27mg**	**36mg**	**54mg**	**72mg**
Cost per day		**£1.04**	**£1.23**	**£1.42**	**£1.23**	**£2.84**
ΔESS relative to solriamfetol 150 mg at	-1.00	Dominated	Dominated	Dominated	Dominated	Dominated
	-2.00	£208,920	£203,860	£198,801	£203,860	£160,985
	-3.00	£74,338	£73,171	£72,003	£73,171	£63,275
	-4.00	£54,679	£54,062	£53,445	£54,062	£48,836
	-5.00	£47,316	£46,904	£46,491	£46,904	£43,410
	-6.00	£39,088	£38,877	£38,665	£38,877	£37,088
	-7.00	£36,280	£36,143	£36,006	£36,143	£34,979

* South-west quadrant of the cost-effectiveness plane (solriamfetol is less costly and less effective).

Table 82. Scenario analysis: solriamfetol 75 mg vs. methylphenidate MR capsules

		Dose of methylphenidate					
		10mg	**20mg**	**30mg**	**40mg**	**50mg**	**60mg**
Cost per day		**£0.83**	**£1.00**	**£1.17**	**£1.92**	**£2.08**	**£2.24**
ΔESS relative to solriamfetol 150 mg at week 8	-1.00	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
	-2.00	£3,572,880	£3,462,646	£3,352,412	£2,866,085	£2,762,336	£2,658,586
	-3.00	£78,035	£76,482	£74,929	£68,078	£66,617	£65,155
	-4.00	£50,649	£49,927	£49,206	£46,023	£45,344	£44,664
	-5.00	£42,014	£41,553	£41,091	£39,054	£38,620	£38,185
	-6.00	£33,213	£32,987	£32,761	£31,766	£31,554	£31,341

	-7.00	£30,388	£30,243	£30,099	£29,461	£29,325	£29,189

* South-west quadrant of the cost-effectiveness plane (solriamfetol is less costly and less effective).

Table 83. Scenario analysis: solriamfetol 150 mg vs. methylphenidate MR capsules

		Dose of methylphenidate					
		10mg	**20mg**	**30mg**	**40mg**	**50mg**	**60mg**
Cost per day		**£0.83**	**£1.00**	**£1.17**	**£1.92**	**£2.08**	**£2.24**
ΔESS relative to solriamfetol 150 mg at week 8	-1.00	£345,673	£339,040	£332,406	£303,140	£296,896	£290,653
	-2.00	£144,104	£141,793	£139,482	£129,286	£127,111	£124,936
	-3.00	£74,409	£73,622	£72,835	£69,361	£68,620	£67,879
	-4.00	£58,278	£57,831	£57,384	£55,413	£54,993	£54,573
	-5.00	£51,603	£51,296	£50,989	£49,633	£49,344	£49,055
	-6.00	£43,717	£43,554	£43,392	£42,676	£42,523	£42,370
	-7.00	£40,900	£40,793	£40,686	£40,215	£40,114	£40,013

* South-west quadrant of the cost-effectiveness plane (solriamfetol is less costly and less effective)

Table 84. Scenario analysis: solriamfetol vs. methylphenidate MR capsules

		Dose of methylphenidate					
		10mg	**20mg**	**30mg**	**40mg**	**50mg**	**60mg**
Cost per day		**£0.83**	**£1.00**	**£1.17**	**£1.92**	**£2.08**	**£2.24**
ΔESS relative to solriamfetol 150 mg at week 8	-1.00	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
	-2.00	£214,513	£209,986	£205,458	£185,485	£181,224	£176,964
	-3.00	£75,629	£74,584	£73,539	£68,930	£67,946	£66,963
	-4.00	£55,360	£54,809	£54,257	£51,822	£51,303	£50,784
	-5.00	£47,772	£47,403	£47,034	£45,406	£45,059	£44,712
	-6.00	£39,321	£39,132	£38,943	£38,110	£37,932	£37,755
	-7.00	£36,432	£36,309	£36,186	£35,644	£35,529	£35,413

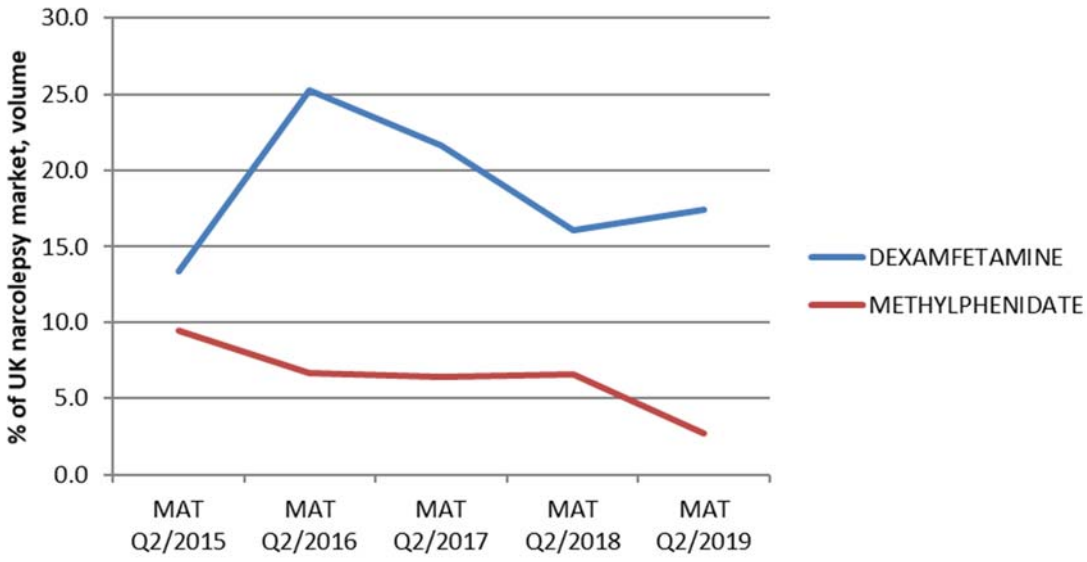
* South-west quadrant of the cost-effectiveness plane (solriamfetol is less costly and less effective)

Whilst this hypothetical analysis indicates that solriamfetol may not be cost-effective when compared to dexamphetamine and methylphenidate the significant limitations with regards to the assumptions should be considered. This hypothetical scenario analysis only considers an impact on the relative impact on ESS relative to solriamfetol 150 mg and does not consider the impact of discontinuation due to TEAS, nor discontinuation due to loss of efficacy associated with either dexamfetamine or methylphenidate due to any comparative efficacy. Hypothetical

scenarios varying these three key parameters (Change in ESS, discontinuation due to TEAE and discontinuation due to lack of efficacy) were not considered to be informative however, the current assumption of equivalent discontinuation rates to solriamfetol are likely to over-estimate the clinical impact of the comparators and so the expected ICERS would likely be much lower than those currently presented.

Data from IQVIA (Figure 25) suggest that dexamfetamine is the predominant amphetamine used in the narcolepsy population at a national level (179), although at a local level there is wide variation. Methylphenidate use has been declining and at the most recent data point (Q2 2019 Moving Annual Total) comprised just 2.7% of the overall narcolepsy market, compared to 17.4% for dexamfetamine. Evidence from the KOL Clinical Practice Interviews suggest that these treatments are typically reserved for patients who have failed modafinil (2).

Figure 25. Market share of dexamfetamine and methylphenidate in the UK narcolepsy treated patients



Abbreviations: MAT, moving annual threshold.
Source: IMS audited SU volume MAT, exported 14/10/2019.

While the current analysis makes assumptions on the impact on EDS, as measured by ESS, with dexamphetamine and methylphenidate it does not consider wider issues such as the rates of discontinuation nor the wider impact on EDS via measures such as MWT. Given that these treatments are older generic medicines (dating back to the 1930s), it could be assumed that, if they were effective and

tolerable, they would have significantly higher market shares. As such, this analysis is likely to significantly over-estimate the potential benefits of both dexamphetamine and methylphenidate and should only be considered as an illustrative analysis in the absence of any robust comparative evidence.

Therefore, given the limitations of the data available for a robust analysis, clinician judgement for each individual patient may be the most appropriate means of deciding between solriamfetol, dexamfetamine and methylphenidate treatment in patients who have failed, are intolerant to or are contraindicated to modafinil. When considering the most suitable treatment option for a given patient, clinicians may also take into account that both methylphenidate and dexamfetamine are Schedule 2 drugs (180).

B.3.8.5 Summary of sensitivity analyses results

The results of PSA were found to be highly congruent with the deterministic base case results and showed that the two doses of solriamfetol would be cost-effective in 99.87% of simulations, assuming a cost-effectiveness threshold of £20,000 per QALY increasing to 99.98% at a cost-effectiveness threshold of £30,000 per QALY.

As expected, the most influential parameters in deterministic sensitivity analysis were the change in ESS relative to solriamfetol 150 mg, due to being the main determinant of treatment efficacy. However, the data is based on robust comparative efficacy data from the ITC hence variations explored do not change the conclusion of the analysis that solriamfetol is the most cost-effective treatment when compared to pitolisant and sodium oxybate. Discontinuation was also shown to be a key driver, but there is minimal data for solriamfetol beyond year one and no data at all for the comparators considered. Despite this the relative impact of these parameters were small and did not make any changes to the overall conclusion of the analysis.

The effects of other model parameters on the base case ICER were found to be modest and the extensive scenario analyses demonstrated the robustness of the base case ICER.

B.3.9 Subgroup analysis

B.3.9.1 Prior modafinil use

This analysis assumed that solriamfetol will be used after modafinil or where it is contraindicated, as modafinil is the established first-line therapy for EDS in narcolepsy. It assumed that solriamfetol would be given to patients who have discontinued modafinil (due to treatment failure or intolerance) or in whom modafinil is contraindicated.

Patients in TONES 2 receiving modafinil prior to trial initiation were discontinued from modafinil such that they had returned to their baseline level of EDS at least 7 days prior to the baseline visit, in the opinion of the Investigator. As such there was a sub-group of patients within the trial that had experienced prior modafinil use. To demonstrate that solriamfetol is effective in reducing EDS and improving wakefulness in patients with narcolepsy irrespective of prior treatment a subgroup analysis was conducted, based on those individuals in TONES 2 who had prior modafinil treatment. The results of this analysis, presented in Table 85 and Table 86, demonstrated that limiting the analysis to those patients with prior modafinil use does not alter the conclusion, and solriamfetol remains a cost-effective treatment compared to both sodium oxybate and pitolisant in patients who have previously used modafinil. This indicates that in addition to being cost-effective in the base case analysis, solriamfetol is also cost-effective within its proposed positioning post-modafinil, within the UK narcolepsy population.

Table 85. Scenario analysis: Prior modafinil use – By dose

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£5,683	13.202	41.960				
Solriamfetol 150mg	£10,389	13.268	41.960	£4,706	0.066	£71,106	£71,106
Sodium Oxybate 4.5g	£11,193	13.140	41.960	£805	-0.128	Dominated	Dominated
Pitolisant <40mg	£20,259	13.268	41.960	£9,066	0.129	£70,337	Extendedly dominated
Sodium Oxybate 6g	£21,480	13.201	41.960	£1,221	-0.068	Dominated	Dominated
Sodium Oxybate 9g	£42,002	13.274	41.960	£20,522	0.073	£281,352	£504,961

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

Table 86. Scenario analysis: Prior modafinil use – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,036	13.235	41.960			
Pitolisant	£20,259	13.268	41.960	£12,223	0.034	£364,568
Sodium oxybate	£24,892	13.205	41.960	£4,633	-0.064	Dominated

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

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Quality assurance: An independent senior health economic modeller, external to the model development, performed quality assurance, which entailed:

- Review of modelling structural assumption and techniques chosen.
- Review of technical deployment (formulas, functionality).
- Review of data inputs and sources.
- Conducting extreme scenario analyses and validation of results.

B.3.11 Interpretation and conclusions of economic evidence

A systematic review of the economic literature did not identify any published economic evaluations for adult patients who suffer from EDS due to narcolepsy that reflected the current decision problem (see Section B.1.1) therefore it was necessary to build upon the learnings from prior economic evaluations to develop the current economic model. The core assumptions of the economic evaluation were informed by the Sleep Services Analysis and KOL Clinical Practice Interviews (see Section B.1.1)

The health economic analysis was driven predominantly by the drug costs associated with the respective treatment costs and the respective changes in ESS from baseline. The current evidence from the clinical trials and the associated ITC show that, the efficacy of the main comparators is broadly comparable, but that solriamfetol is significantly cheaper than both pitolisant and sodium oxybate. The base case analysis considers an assessment of response at 8-weeks, this was done to reflect the best available data for the comparators and demonstrates that solriamfetol is cost-effective when compared to both pitolisant and sodium oxybate. Utilising the data for the primary endpoint of the pivotal phase 3 RCT, TONES 2, for solriamfetol results in both doses forming the cost-effectiveness frontier, further enhancing the cost-effectiveness of solriamfetol. In clinical practice the time between routine follow-up assessments/visits can vary significantly however, the current analysis demonstrates that allowing clinicians flexibility when assessing response, be this based on clinical judgement or limited capacity within the service (2), will not

impact the cost-effectiveness of solriamfetol. Extensive sensitivity analysis has also demonstrated the robustness of the ICERs associated with solriamfetol when compared to pitolisant and sodium oxybate.

The cost-effectiveness analysis was performed using ESS scores, which is commonly used in clinical practice to assess response to treatment in patients with EDS due to narcolepsy. Using this particular outcome measures may have underestimated the true cost-effectiveness of solriamfetol as the efficacy analyses on the objective MWT in the ITC (see Section B.2.9) demonstrated a more significant improvement on this objective outcome for solriamfetol 150 mg versus pitolisant than was demonstrated by the ESS. Accordingly, the current approach to assessing cost-effectiveness using ESS may be seen as conservative. Furthermore, although the introduction of solriamfetol is not anticipated to require any additional resource use compared with any existing treatment for EDS in narcolepsy (2), it is expected to require less resource use compared with dexamfetamine and methylphenidate, both of which require ongoing monitoring of psychiatric and cardiovascular status(as per their respective SmPCs) (63, 64, 68). These points suggest that there may be additional cost-effectiveness associated with solriamfetol that has not been captured in the current model.

The absence of robust clinical evidence for dexamphetamine and methylphenidate precludes any robust or meaningful comparative analysis to be conducted. Following the widely accepted first line treatment of modafinil, there is no consistent nor established position of any of the comparator treatments defined in the company submission. Treatments are either relatively new but costly (pitolisant, sodium oxybate), or older medicines (dexamphetamine, methylphenidate) dating back originally to the 1930s. Despite being a novel product, with RCT evidence across both objective and subjective measures, the pricing of solriamfetol is more consistent with the older treatment options than the newer compounds. Therefore, given the limitations of the data available for a robust analysis, clinician judgement for each individual patient may be the most appropriate means of deciding between solriamfetol, dexamfetamine and methylphenidate treatment in patients who have failed, are intolerant to or are contraindicated to modafinil. When considering the

most suitable treatment option for a given patient, clinicians may take into account that both methylphenidate and dexamfetamine are Schedule 2 drugs (180).

The base case analysis demonstrates that solriamfetol is highly cost-effective versus the main comparators of pitolisant (which is marginally more effective, as measured using ESS, but more costly resulting in an ICER for pitolisant of £357,669) and sodium oxybate which is dominated (less effective, as measured using ESS, and more costly than solriamfetol) and utilising the primary end-point data results in solriamfetol dominating both pitolisant and sodium oxybate. As such, solriamfetol offers highly cost-effective use of NHS resources, in a difficult to treat cohort who have significant unmet need for treatment of their EDS.

References

1. Jazz Pharmaceuticals. **CONFIDENTIAL.** Exploring sleep services within the NHS - Supplementary Market Research Insights. 2019.
2. Jazz Pharmaceuticals. **CONFIDENTIAL.** KOL Clinical Practice Interviews. . 2019.
3. National Institute for Health and Care Excellence. Narcolepsy with or without cataplexy in adults: pitolisant. Evidence summary [ES8] 2017. Available from: https://www.nice.org.uk/advice/es8/resources/narcolepsy-with-or-without-cataplexy-in-adults-pitolisant-pdf-32181397189. Accessed on: 7 January 2020
4. Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30(12):1705-11.
5. National Institute of Neurological Disorders and Stroke. Narcolepsy fact sheet. 2018. Available from: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet. Accessed on: 7 January 2020
6. Nishino S. Clinical and neurobiological aspects of narcolepsy. Sleep Med. 2007;8(4):373-99.
7. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. The Lancet. 2007;369(9560):499-511.
8. Peacock J, Benca R. Narcolepsy : clinical features, co-morbidities & treatment. Indian Journal of Medical Research. 2010;131(2):338-49.
9. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387-94.
10. Committee on Sleep Medicine and Research (Board on Health Sciences Policy). Ch 3. Extent and Health Consequences of Chronic Sleep Loss and Sleep Disorders. In: Colten HR, Altevogt BM, editors. Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. Washington DC, USA: The National Academies Press,; 2006.
11. Billiard M, Dauvilliers Y, Dolenc-Grošelj L, Lammers GJ, Mayer G, Sonka K. Ch 38. Management of Narcolepsy in Adults. In: Gilus N, Barnes M, Brainin M, editors. European Handbook of Neurological Management. 1. 2nd ed. Chichester, West Sussex, United Kingdom: John Wiley & Sons; 2011. p. 513-28.
12. National Health Service. Narcolepsy - Overview. 2019. Available from: https://www.nhs.uk/conditions/narcolepsy/. Accessed on: 7 January 2020
13. Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, Mayer G, et al. EFNS guidelines on management of narcolepsy. Eur J Neurol. 2006;13(10):1035-48.
14. Kane N. Sodium oxybate for the treatment of narcolepsy with cataplexy in adults. 2017.
15. Roth T, Dauvilliers Y, Mignot E, Montplaisir J, Paul J, Swick T, et al. Disrupted nighttime sleep in narcolepsy. J Clin Sleep Med. 2013;9(9):955-65.
16. Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. Sleep Med. 2015;16(1):9-18.
17. Abad VC, Guilleminault C. New developments in the management of narcolepsy. Nature and science of sleep. 2017;9(9):39-57.

18. Narcolepsy UK. About Narcolepsy. 2019. Available from: https://www.narcolepsy.org.uk/about-narcolepsy. Accessed on: 7 January 2020
19. Ohayon MM, Priest RG, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. Neurology. 2002;58(12):1826-33.
20. Longstreth WT, Jr., Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. Sleep. 2007;30(1):13-26.
21. Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. Vaccine. 2013;31(8):1246-54.
22. Dauvilliers Y, Montplaisir J, Molinari N, Carlander B, Ondze B, Besset A, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. Neurology. 2001;57(11):2029-33.
23. Thorpy MJ, Hiller G. The medical and economic burden of narcolepsy: implications for managed care. Am Health Drug Benefits. 2017;10(5):233-41.
24. Thorpy M, Morse AM. Reducing the clinical and socioeconomic burden of narcolepsy by earlier diagnosis and effective treatment. Sleep medicine clinics. 2017;12(1):61-71.
25. Teixeira VG, Faccenda JF, Douglas NJ. Functional status in patients with narcolepsy. Sleep Med. 2004;5(5):477-83.
26. Narcolepsy UK. Narcolepsy Charter. 2019. Available from: https://www.narcolepsy.org.uk/sites/narcolepsy.org.uk/files/resources/files/NUK_Charter_v12%28withQR%29.pdf. Accessed on: 7 January 2020
27. Ingravallo F, Gnucci V, Pizza F, Vignatelli L, Govi A, Dormi A, et al. The burden of narcolepsy with cataplexy: how disease history and clinical features influence socio-economic outcomes. Sleep Med. 2012;13(10):1293-300.
28. Jennum P, Ibsen R, Kjellberg J. Long-term health and socioeconomic consequences of childhood and adolescent-onset of narcolepsy. Sleep Medicine. 2019.
29. Szakacs A, Chaplin JE, Tideman P, Stromberg U, Nilsson J, Darin N, et al. A population-based and case-controlled study of children and adolescents with narcolepsy: Health-related quality of life, adaptive behavior and parental stress. Eur J Paediatr Neurol. 2019;23(2):288-95.
30. Plazzi G, Clawges HM, Owens JA. Clinical characteristics and burden of illness in pediatric patients with narcolepsy. Pediatric neurology. 2018;85:21-32.
31. Narcolepsy UK. Narcolepsy need-to-know guide: For teachers. 2015. Available from: https://www.narcolepsy.org.uk/sites/narcolepsy.org.uk/files/files/Narcolepsy%20Need-to-Know%20Guide%20-%20For%20Teachers.pdf. Accessed on: 7 January 2020
32. Maski K, Steinhart E, Williams D, Scammell T, Flygare J, McCleary K, et al. Listening to the patient voice in narcolepsy: diagnostic delay, disease burden, and treatment efficacy. J Clin Sleep Med. 2017;13(3):419-25.

33. Kapella MC, Berger BE, Vern BA, Vispute S, Prasad B, Carley DW. Health-related stigma as a determinant of functioning in young adults with narcolepsy. PLoS One. 2015;10(4):e0122478.
34. Sahni AS, Carlucci M, Malik M, Prasad B. Management Of Excessive Sleepiness In Patients With Narcolepsy And OSA: Current Challenges And Future Prospects. Nature and science of sleep. 2019;11:241-52.
35. Jennum P, Ibsen R, Petersen ER, Knudsen S, Kjellberg J. Health, social, and economic consequences of narcolepsy: a controlled national study evaluating the societal effect on patients and their partners. Sleep Med. 2012;13(8):1086-93.
36. Shneerson JM, Dauvilliers YA, Plazzi G, Myers AJ, Garcia-Borreguero D. The Impact of Narcolepsy and Its Treatment – A European Study. European Neurological Review. 2008;3(2).
37. David A, Constantino F, dos Santos JM, Paiva T. Health-related quality of life in Portuguese patients with narcolepsy. Sleep Med. 2012;13(3):273-7.
38. Campbell AJ, Signal TL, O'Keeffe KM, Bakker JP. Narcolepsy in New Zealand: pathway to diagnosis and effect on quality of life. N Z Med J. 2011;124(1336):51-61.
39. Ozaki A, Inoue Y, Hayashida K, Nakajima T, Honda M, Usui A, et al. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naive patients and the general Japanese population. Sleep Med. 2012;13(2):200-6.
40. Vignatelli L, Plazzi G, Peschechera F, Delaj L, D'Alessandro R. A 5-year prospective cohort study on health-related quality of life in patients with narcolepsy. Sleep Med. 2011;12(1):19-23.
41. Ervik S, Abdelnoor M, Heier MS, Ramberg M, Strand G. Health-related quality of life in narcolepsy. Acta neurologica Scandinavica. 2006;114(3):198-204.
42. Wu S, Wang R, Ma X, Zhao Y, Yan X, He J. Excessive daytime sleepiness assessed by the Epworth Sleepiness Scale and its association with health related quality of life: a population-based study in China. BMC Public Health. 2012;12:849.
43. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young Adults. Biological Psychiatry. 1996;39(6):411-8.
44. Flores NM, Villa KF, Black J, Chervin RD, Witt EA. The humanistic and economic burden of narcolepsy. J Clin Sleep Med. 2016;12(3):401-7.
45. Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Medicine. 2004;5(1):37-41.
46. Black J, Reaven NL, Funk SE, McGaughey K, Ohayon M, Guilleminault C, et al. The Burden of Narcolepsy Disease (BOND) study: health-care utilization and cost findings. Sleep Med. 2014;15(5):522-9.
47. Ohayon M, Pasta D, Cisternas MG, Williams M, Carls G, Black J, et al., editors. Injuries, motor vehicle accidents, and near misses in narcolepsy: results from the Nexus Narcolepsy Registry. 32nd Annual Meeting of the Associated Professional Sleep Societies; 2018 Jun 2-6,; Baltimore, MD.

48. Carlton R, Lunacsek O, Regan T, Carroll CA. Healthcare costs among patients with excessive sleepiness associated with obstructive sleep apnea, shift work disorder, or narcolepsy. Am Health Drug Benefits. 2014;7(6):334.
49. Leschziner G. Narcolepsy: a clinical review. Pract Neurol. 2014;14(5):323-31.
50. Dunne L, Patel P, Maschauer EL, Morrison I, Riha RL. Misdiagnosis of narcolepsy. Sleep Breath. 2016;20(4):1277-84.
51. Dodel R, Peter H, Walbert T, Spottke A, Noelker C, Berger K, et al. The socioeconomic impact of narcolepsy. Sleep. 2004;27(6):1123-8.
52. National Health Service. Narcolepsy - Treatment. National Health Service; 2019. Available from: https://www.nhs.uk/conditions/narcolepsy/treatment/. Accessed on: 7 January 2020
53. National Institute for Health and Care Excellence. NG127 Suspected neurological conditions: recognition and referral. 2019. Available from: https://www.nice.org.uk/guidance/ng127/resources/suspected-neurological-conditions-recognition-and-referral-pdf-66141663923653. Accessed on: 7 January 2020
54. Thakrar C, Patel K, D'Ancona G, Kent BD, Nesbitt A, Selsick H, et al. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. J Sleep Res. 2018;27(4):e12627.
55. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998;43(1):88-97.
56. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology. 2000;54(5):1166-75.
57. Regional Medicines Optimisation Committee. Commissioning in adult patients with narcolepsy with cataplexy. 2019. Available from: https://www.sps.nhs.uk/articles/rmoc-sodium-oxybate-in-adult-patients/. Accessed on: 7 January 2020
58. Northern Treatment Advisory Group. Pitolisant for Narcolepsy Treatment Pathway. 2018. Available from: http://ntag.nhs.uk/docs/NTAG%20Pitolisant%20Pathway%20-%20final.pdf. Accessed on: 7 January 2020
59. Pan Mersey Area Prescribing Committee. Narcolepsy. University Hospital Aintree Sleep Service Pathway. 2019. Available from: https://www.panmerseyapc.nhs.uk/media/2178/narcolepsy.pdf. Accessed on: 7 January 2020
60. South East London Area Prescribing Committee. Pathway for the pharmacological management of excessive daytime sleepiness due to narcolepsy. 2018. Available from: http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Clinical%20guidelines%20and%20pathways/SLEEP%20Narcolepsy%20pathway%20Aug%202018.pdf. Accessed on: 7 January 2020
61. Bisagno V, Gonzalez B, Urbano FJ. Cognitive enhancers versus addictive psychostimulants: The good and bad side of dopamine on prefrontal cortical circuits. Pharmacol Res. 2016;109:108-18.

62. Guy's and St Thomas' NHS Foundation Trust. Methylphenidate for the treatment of narcolepsy. 2018. Available from: https://www.guysandstthomas.nhs.uk/resources/patient-information/pharmacy/methylphenidate.pdf. Accessed on: 7 January 2020
63. Brown & Burk UK Ltd. Dexamfetamine sulfate 5mg tablets summary of product characteristics 2019. Available from: http://www.mhra.gov.uk/spc-pil/?subsName=DEXAMFETAMINE%20SULFATE&pageID=SecondLevel. Accessed on: 7 January 2020
64. Martindale Pharmaceuticals Ltd. Dexamfetamine sulfate 1mg/ml oral solution summary of product characteristics 2018. Available from: http://www.mhra.gov.uk/spc-pil/?subsName=DEXAMFETAMINE%20SULFATE&pageID=SecondLevel. Accessed on: 7 January 2020
65. Teva UK Limited. Modafinil summary of product characteristics,. 2017. Available from: https://www.medicines.org.uk/emc/product/5412/smpc. Accessed on: 7 January 2020
66. UCB Pharma. Xyrem (500mg/ml) Sodium oxybate summary of product characteristics. 2019. Available from: https://www.medicines.org.uk/emc/product/178. Accessed on: 7 January 2020
67. Lincoln Medical Ltd. Pitolisant (Wakix) summary of product characteristics. 2016. Available from: https://www.medicines.org.uk/emc/product/7402. Accessed on: 7 January 2020
68. Electronic Medicines Compendium. Methylphenidate summary of product characteristics. 2017. Available from: https://www.medicines.org.uk/emc/search?q=methylphenidate. Accessed on: 7 January 2020
69. Maruff P, Falleti MG, Collie A, Darby D, McStephen M. Fatigue-related impairment in the speed, accuracy and variability of psychomotor performance: comparison with blood alcohol levels. J Sleep Res. 2005;14(1):21-7.
70. Williamson AM, Feyer AM. Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication. Occup Environ Med. 2000;57(10):649-55.
71. Gov.uk. The drink drive limit. 2019. Available from: https://www.gov.uk/drink-drive-limit. Accessed on: 7 January 2020
72. Narcolepsy UK. Narcolepsy need-to-know guide: Driving. 2019. Available from: https://www.narcolepsy.org.uk/sites/narcolepsy.org.uk/files/files/Narcolepsy%20Need-to-Know%20Guide%20-%20Driving%202018-04-05.pdf. Accessed on: 7 January 2020
73. Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. Journal of Sleep Research. 2001;10(1):75-81.
74. Bogan RK, Feldman N, Emsellem HA, Rosenberg R, Lu Y, Bream G, et al. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. Sleep Med. 2015;16(9):1102-8.
75. Ruoff C, Swick TJ, Doekel R, Emsellem HA, Feldman NT, Rosenberg R, et al. Effect of Oral JZP-110 (ADX-N05) on Wakefulness and Sleepiness in Adults with Narcolepsy: A Phase 2b Study. Sleep. 2016;39(7):1379-87.

76. Jazz Pharmaceuticals. **CONFIDENTIAL.** TONES 2 Clinical study report. A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy. . 2017.
77. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3):359-70.
78. Dauvilliers Y, Shapiro C, Mayer G, Lammers GJ, Emsellem H, Plazzi G, et al., editors. Oral Presentation: Solriamfetol (JZP-110) for Treatment of Excessive Sleepiness in Narcoleptic Patients With and Without Cataplexy: Results From a Randomized, Phase 3 Clinical Trial. Sleep, the 32nd Annual Meeting of the Associated Professional Sleep Societies; 2018 June 2-6 2018; Baltimore, MD.
79. Emsellem HA, Thorpy MJ, Lammers GJ, Shapiro CM, Mayer G, Plazzi G, et al. Measures of Functional Outcomes, Work Productivity, and Quality of Life From a Randomized, Phase 3 Study of Solriamfetol in Participants With Narcolepsy. Sleep Medicine. 2019.
80. Rosenberg R, Baladi M, Menno D, Bron M, editors. Poster G25: Clinically relevant effects of solriamfetol (JZP-110) on excessive sleepiness: a post hoc analysis of the magnitude of change in clinical trials in adults with narcolepsy or obstructive sleep apnea. Academy of Managed Care Pharmacy Nexus 2018 22-25 October 2018; Orlando, Florida.
81. Thorpy M, Dauvilliers Y, Shapiro C, Mayer G, Corser B, Chen D, et al. Poster 092: A Randomized, Placebo-Controlled, Phase 3 Study of the Safety and Efficacy of Solriamfetol (JZP-110) for the Treatment of Excessive Sleepiness in Patients With Narcolepsy. Presented at WorldSleep 2017, a Joint Congress of World Association of Sleep Medicine and World Sleep Federation, Oct 7-11, Prague, Czech Republic. 2017.
82. Thorpy M, Dauvilliers Y, Lammers GJ, Shapiro C, Mayer G, Plazzi G, et al. Poster 140: Quality of Life, Functional Evaluation, and Work Productivity in Patients With Narcolepsy: Results From a Phase 3 Study of Solriamfetol (JZP-110). Presented at US Psychiatric and Mental Health Congress, Oct 25-28, Orlando FL. 2018.
83. Jazz Pharmaceuticals. **CONFIDENTIAL.** TONES 1: Clinical Study Report (ADX-N05 Study 202). 2014.
84. Jazz Pharmaceuticals. **CONFIDENTIAL**. TONES 5 Clinical study report. A long-term safety and maintenance of efficacy study of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy or obstructive sleep apnoea. . 2018.
85. Malhotra A, Shapiro C, Pepin JL, Hedner J, Ahmed M, Foldvary-Schaefer N, et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. Sleep. 2019.
86. Weaver TE, Pepin J, Schwab R, Shapiro C, Hedner J, Ahmed M, et al., editors. Poster 221: Long-Term Effects of Solriamfetol on Quality of Life in Participants With Excessive Daytime Sleepiness Associated With Narcolepsy or Obstructive Sleep Apnea. Sleep,; 2019 June 8 - 12 2019; San Antonio, TX.

87. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000;9(1):5-11.
88. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.
89. National Institute for Health and Care Excellence. Obstructive sleep apnoea syndrome, Clinical Knowledge Summary. 2015. Available from: https://cks.nice.org.uk/obstructive-sleep-apnoea-syndrome#!diagnosisAdditional. Accessed on: 10 December 2019
90. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, et al. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2018;197(7):961-3.
91. Lammers G, Bogan R, Schweitzer PK, Menno D, Carter J, Bron M, et al., editors. Oral Presentation 32: Thresholds for Clinically Meaningful Changes on the Epworth Sleepiness Scale and Maintenance of Wakefulness Test Sleep Latency World Sleep 2019; 2019 20 - 25 September 2019; Vancouver, Canada.
92. Scrima L, Emsellem HA, Becker PM, Ruoff C, Lankford A, Bream G, et al. Identifying clinically important difference on the Epworth Sleepiness Scale: results from a narcolepsy clinical trial of JZP-110. Sleep Med. 2017;38:108-12.
93. Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. Electroencephalogr Clin Neurophysiol. 1982;53(6):658-61.
94. Doghramji K, Mitler MM, Sangal RB, Shapiro C, Taylor S, Walsleben J, et al. A normative study of the maintenance of wakefulness test (MWT). Electroencephalogr Clin Neurophysiol. 1997;103(5):554-62.
95. Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep. 2005;28(1):113-21.
96. Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP, et al. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3). A Randomized Controlled Trial. Am J Respir Crit Care Med. 2019;199(11):1421-31.
97. Strollo PJ, Jr., Hedner J, Collop N, Lorch DG, Jr., Chen D, Carter LP, et al. Solriamfetol for the Treatment of Excessive Sleepiness in OSA: A Placebo-Controlled Randomized Withdrawal Study. Chest. 2019;155(2):364-74.
98. Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. Sleep. 2009;32(7):915-9.
99. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. J Epidemiol Community Health. 1999;53(1):46-50.
100. The EuroQol Group. EQ-5D-5L User Guide. Version 3.0. 2019. Available from: https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf. Accessed on: 7 January 2020

101. Reilly MC. Work Productivity and Activity Impairment Questionnaire scoring. 1993. Available from: http://www.reillyassociates.net/WPAI_Scoring.html. Accessed on: 7 January 2020
102. Reilly MC. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP). 1993. Available from: http://www.reillyassociates.net/WPAI_SHP.html. Accessed on: 7 January 2020
103. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65.
104. Ware Jr JE, Kosinski M, Bjorner JB, Turner-Bowker D, Maruish ME. User's Manual for the SF-36v2™ Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated; 2007.
105. Bogan RK, Black J, Swick T, Mamelak M, Kovacevic-Ristanovic R, Villa KF, et al. Correlation of Changes in Patient-Reported Quality of Life With Physician-Rated Global Impression of Change in Patients With Narcolepsy Participating in a Clinical Trial of Sodium Oxybate: A Post Hoc Analysis. Neurology and therapy. 2017;6(2):237-45.
106. Thorpy M, Shapiro C, Mayer G, Corser B, Chen D, Li J, et al., editors. Poster M222: A Randomized, Placebo-Controlled, Phase 3 Study of Solriamfetol (JZP-110) in Patients With Narcolepsy: Effects on Wakefulness, Excessive Sleepiness, and Health-Related Quality-of-Life. 56th Annual Meeting of the American College of Neuropsychopharmacology; 2017; Palm Springs, California.
107. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol. 2013;12(11):1068-75.
108. Szakacs Z, Dauvilliers Y, Mikhaylov V, Poverennova I, Krylov S, Jankovic S, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(3):200-7.
109. US Xyrem® Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep. 2002;25(1):42-9.
110. Bogan RK, Roth T, Schwartz J, Miloslavsky M. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. J Clin Sleep Med. 2015;11(4):427-32.
111. Xyrem® International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med. 2005;1(4):391-7.
112. Xyrem® International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. Sleep Med. 2005;6(5):415-21.
113. Bogan RK, Swick T, Mamelak M, Kovacevic-Ristanovic R, Lai C, Black J, et al. Evaluation of quality of life in patients with narcolepsy treated with sodium oxybate: use of the 36-Item Short-Form health survey in a clinical trial. Neurology and therapy. 2016;5(2):203-13.

114. Weaver T, Cuellar N. A randomized trial evaluating the effectiveness of sodium oxybate therapy on quality of life in narcolepsy. Sleep. 2006;29(9):1189-94.
115. Black J, Houghton W. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep. 2006;29(7):939-46.
116. Ades AE, Caldwell DM, Reken S, Welton NJ, Sutton AJ, Dias S. NICE Decision Support Unit Technical Support Documents. London: National Institute for Health and Care Excellence (NICE); 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395872/. Accessed on: 7 January 2020
117. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2002;64(4):583-639.
118. European Medicines Agency. Modafinil. 2011. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/modafinil. Accessed on: 7 January 2020
119. Balk E, Earley A, Patel K, Trikalinos T, Dahabreh I. Empirical assessment of within-arm correlation imputation in trials of continuous outcomes. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK115797/. Accessed on: 7 January 2020
120. The Cochrane Collaboration. Imputing standard deviations for changes from baseline. 2011. Available from: https://handbook-5-1.cochrane.org/chapter_16/16_1_3_2_imputing_standard_deviations_for_changes_from_baseline.htm. Accessed on: 7 January 2020
121. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(1):13.
122. Carter LP, Henningfield JE, Wang YG, Lu Y, Kelsh D, Vince B, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the human abuse liability of solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor. J Psychopharmacol. 2018;32(12):1351-61.
123. Baladi MG, Forster MJ, Gatch MB, Mailman RB, Hyman DL, Carter LP, et al. Characterization of the Neurochemical and Behavioral Effects of Solriamfetol (JZP-110), a Selective Dopamine and Norepinephrine Reuptake Inhibitor. J Pharmacol Exp Ther. 2018;366(2):367-76.
124. Harvard Medical School: Division of sleep medicine. Narcolepsy: Medications. 2018. Available from: http://healthysleep.med.harvard.edu/narcolepsy/treating-narcolepsy/medications. Accessed on: 7 January 2020
125. Schwartz JRL, Feldman NT, Bogan RK, Nelson MT, Hughes RJ. Dosing Regimen Effects of Modafinil for Improving Daytime Wakefulness in Patients With Narcolepsy. Clinical Neuropharmacology. 2003;26(5):252-7.
126. Jazz Pharmaceuticals USA. Sodium oxybate prescribing information,. 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021196s013lbl.pdf. Accessed on: 7 January 2020

10 December 2019.

127. Dean B, Aguilar D, Shapiro C, Orr WC, Isserman JA, Calimlim B, et al. Impaired health status, daily functioning, and work productivity in adults with excessive sleepiness. Journal of occupational and environmental medicine. 2010;52(2):144-9.
128. Food and Drug Administration. Drug study designs: Guidance for institution review board and clinical investigators. 1998. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-study-designs. Accessed on: 7 January 2020
129. Parkes J, Chen S, Clift S, Dahlitz M, Dunn G. The clinical diagnosis of the narcoleptic syndrome. Journal of Sleep Research. 1998;7(1):41-52.
130. Weaver TE, Mathias SD, Crosby RD, Bron M, Bujanover S, Menno D, et al. **CONFIDENTIAL**: Relationship Between Sleep Efficacy Endpoints and Measures of Functional Status and Health-Related Quality of Life in Patients With Narcolepsy or Obstructive Sleep Apnea Treated for Excessive Sleepiness. 2020.
131. American Thoracic Society. Functional Outcomes of Sleep Questionnaire (FOSQ). 2014. Available from: https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/fosq.php. Accessed on: 7 January 2020
132. Bolin K, Berling P, Wasling P, Meinild H, Kjellberg J, Jennum P. The cost-utility of sodium oxybate as narcolepsy treatment. Acta neurologica Scandinavica. 2017;136(6):715-20.
133. Lanting L, Roome C, Lang L, Stein K. Sodium oxybate for narcolepsy with cataplexy - A cost-effective analysis. Journal of Neuroinfectious Diseases. 2014;5:2.
134. Tatar M, Tuna E, Caglayan B, Sarica N, Firidin A. Cost effectiveness of sodium oxybate in treatment of cataplexy in patients with narcolepy in turkey. Value in Health. 2015;18 (7):A757.
135. Scottish Medicines Consortium. Sodium oxybate 500mg/ml oral solution (Xyrem), resubmission, September 2007 [online]. 2007. Available from: https://www.scottishmedicines.org.uk/medicines-advice/sodium-oxybate-500mgml-oral-solution-xyrem-resubmission-24606/ Accessed on: 7 January 2020
136. Canadian Agency for Drugs and Technologies in Health. Sodium oxybate, resubmission, January 2009. 2009. Available from: https://www.cadth.ca/sodium-oxybate-12. Accessed on: 7 January 2020
137. Scottish Medicines Consortium. Sodium oxybate 500mg/ml oral solution (Xyrem), full submission, April 2006 [online]. . 2006. Available from: https://www.scottishmedicines.org.uk/medicines-advice/sodium-oxybate-500mgml-oral-solution-xyrem-fullsubmission-24606/. Accessed on: 7 January 2020
138. National Institute for Health and Care Excellence. TA139 Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome 2008. Available from: https://www.nice.org.uk/guidance/ta139/resources/continuous-positive-airway-pressure-for-the-treatment-of-obstructive-sleep-apnoeahypopnoea-syndrome-pdf-82598202209221. Accessed on: 7 January 2020

139. McDaid C, Griffin S, Weatherly H, Duree K, Van der Burgt M, Van Hout S, et al. NICE TA139 Assessment report: The Continuous Positive Airway Pressure for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. 2007.
140. National Institute for Health and Care Excellence. Obstructive sleep apnoea syndrome. 2015. Available from: https://cks.nice.org.uk/obstructive-sleep-apnoea-syndrome#!diagnosisAdditional. Accessed on: 7 January 2020
141. Ayas NT, FitzGerald JM, Fleetham JA, White DP, Schulzer M, Ryan CF, et al. Cost-effectiveness of continuous positive airway pressure therapy for moderate to severe obstructive sleep apnea/hypopnea. Arch Intern Med. 2006;166(9):977-84.
142. Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. The clinical use of the MSLT and MWT. Sleep. 2005;28(1):123-44.
143. Gov.uk. Medical conditions, disabilities and driving. 2019. Available from: https://www.gov.uk/driving-medical-conditions. Accessed on: 7 January 2020
144. Department for Transport. Reported road casualties in Great Britain: 2018 annual report2019 4th December 2019. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/834585/reported-road-casualties-annual-report-2018.pdf.
145. Gov.uk. Vehicle mileage and occupancy. 2019. Available from: https://www.gov.uk/government/statistical-data-sets/nts09-vehicle-mileage-and-occupancy Accessed on: 7 January 2020
146. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 (PMG9). 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed on: 7 January 2020
147. Office of National Statistics. National Life Tables, 2015-2017. 2018. Available from: https://www.ons.gov.uk/releases/nationallifetablesuk2015to2017 Accessed on: 7 January 2020
148. Ohayon MM, Black J, Lai C, Eller M, Guinta D, Bhattacharyya A. Increased mortality in narcolepsy. Sleep. 2014;37(3):439-44.
149. Chakravorty I, Cayton RM, Szczepura A. Health utilities in evaluating intervention in the sleep apnoea/hypopnoea syndrome. Eur Respir J. 2002;20(5):1233-8.
150. Mar J, Rueda JR, Duran-Cantolla J, Schechter C, Chilcott J. The cost-effectiveness of nCPAP treatment in patients with moderate-to-severe obstructive sleep apnoea. Eur Respir J. 2003;21(3):515-22.
151. Tousignant P, Cosio MG, Levy RD, Groome PA. Quality adjusted life years added by treatment of obstructive sleep apnea. Sleep. 1994;17(1):52-60.
152. Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. J Sleep Res. 1997;6(3):199-204.
153. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Long-term benefits in self-reported health status of nasal continuous positive airway pressure therapy for obstructive sleep apnoea. QJM. 2001;94(2):95-9.
154. National Health Service. National Drug Tariff. 2019. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff. Accessed on: 7 January 2020

155. Curtis L, Burns A. Unit Costs of Health and Social Care 2018, Personal Social Services Research Unit, University of Kent, Canterbury. 2018.
156. Gray A, Clarke P, Wolstenholme K, Wordsworth S. Applied Methods of Cost-effectiveness Analysis in Healthcare. Handbooks in Health Economic Evaluation, volume 3. 2010.
157. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep. 2010;33(5):585-92.
158. Yang Y, Brazier J, Tsuchiya A. Effect of adding a sleep dimension to the EQ-5D descriptive system: a "bolt-on" experiment. Med Decis Making. 2014;34(1):42-53.
159. Bowling A. What things are important in people's lives? A survey of the public's judgements to inform scales of health related quality of life. Soc Sci Med. 1995;41(10):1447-62.
160. Hawton A, Green C, Dickens AP, Richards SH, Taylor RS, Edwards R, et al. The impact of social isolation on the health status and health-related quality of life of older people. Qual Life Res. 2011;20(1):57-67.
161. Dodel R, Peter H, Spottke A, Noelker C, Althaus A, Siebert U, et al. Health-related quality of life in patients with narcolepsy. Sleep Medicine. 2007;8(7-8):733-41.
162. Althoff T, Sosic R, Hicks JL, King AC, Delp SL, Leskovec J. Large-scale physical activity data reveal worldwide activity inequality. Nature. 2017;547(7663):336-9.
163. Chhangani BS, Roehrs TA, Harris EJ, Hyde M, Drake C, Hudgel DW, et al. Pain sensitivity in sleepy pain-free normals. Sleep. 2009;32(8):1011-7.
164. Bernard SA, Chelminski PR, Ives TJ, Ranapurwala SI. Management of Pain in the United States-A Brief History and Implications for the Opioid Epidemic. Health Serv Insights. 2018;11:1178632918819440.
165. Stephenson J. Veterans' Pain a Vital Sign. JAMA. 1999;281(11):978.
166. Stepnowsky C, Sarmiento K, Bujanover S, Villa KF, Li V, Flores NM. Comorbidities, health-related quality of life, and work productivity among people with obstructive sleep apnea with excessive sleepiness: findings from the 2016 US National Health and Wellness Survey (NHWS). J Clin Sleep Med. 2019;15(2):235-43.
167. Govi A, Gnucci V, Vignatelli L, Zenesini C, Ventrucci C, Pizza F, et al. A pragmatic approach to test the reliability of a classification of permanent impairment due to narcolepsy. Journal of Sleep Research Conference: 23rd Congress of the European Sleep Research Society, ESRS. 2016;25(Supplement 1).
168. Dauvilliers Y, Beziat S, Pesenti C, Lopez R, Barateau L, Carlander B, et al. Measurement of narcolepsy symptoms: the Narcolepsy Severity Scale. Neurology. 2017;88(14):1358-65.
169. Villa KF, Black J, Chervin R, Flores N, Witt EA. Humanistic burden of narcolepsy: Results from the national health and wellness survey. Sleep Conference: 29th Annual Meeting of the Associated Professional Sleep Societies, LLC, SLEEP. 2015;38(SUPPL. 1).

170. West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. The effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes [personal communication]. Thorax. 2007;62(11):969-74.
171. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet. 2002;359(9302):204-10.
172. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of health economics. 2002;21(2):271-92.
173. Dolan P, Gudex C, Kind P, Williams A. A Social Tariff for Euroqol: Results From a UK General Population Survey. York: University of York Centre for Health Economics. 1995.
174. British National Formulary. Pitolisant. 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/pitolisant.html. Accessed on: 7 January 2020
175. British National Formulary. Sodium Oxybate. 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/sodium-oxybate.html. Accessed on: 7 January 2020
176. World Health Organisation. Sodium Oxybate Defined Daily Dose. 2019. Available from: https://www.whocc.no/atc_ddd_index/?code=N07XX04&showdescription=yes. Accessed on: 7 January 2020
177. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. American journal of epidemiology. 2011;173(6):676-82.
178. British National Formulary. Methylphenidate Hydrochloride. 2019. Available from: https://bnf.nice.org.uk/drug/methylphenidate-hydrochloride.html. Accessed on: 7 January 2020
179. Jazz Pharmaceuticals. CONFIDENTIAL. Data on File: IQVIA BPI MIDAS data 2019.
180. Gov.uk. Guidance: List of most commonly encountered drugs currently controlled under the misuse of drugs legislation. 2019. Available from: https://www.gov.uk/government/publications/controlled-drugs-list--2/list-of-most-commonly-encountered-drugs-currently-controlled-under-the-misuse-of-drugs-legislation. Accessed on: 7 January 2020

B.4 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: TONES additional trial information

Appendix M: NHWS analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

File name	Version	Contains confidential information	Date
ID1602_Updated clarification letter_Redacted_26Nov	2.0	Yes	26th November 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Trial patient characteristics

A1. The Company submission (CS) reports that in the TONES 2 trial, almost half of patients had prior use of modafinil ([redacted] placebo; [redacted] combined solriamfetol).

a) Please clarify whether modafinil was the first line of treatment in these patients, and for what reason modafinil was discontinued (if known).

Data were not collected regarding either of these characteristics, so it is not possible to provide answers.

b) For what reason did patients not receive modafinil prior to inclusion in the trial if known (e.g. contraindication)?

Reasons for use or non-use of modafinil were not documented as part of the study inclusion criteria. Almost half of included patients had used modafinil previously and approximately [redacted] used some form of stimulant treatment prior to study entry.

However, as nearly half of TONES 2 patients had received prior treatment with modafinil and approximately a further quarter had received treatment with armodafinil, which is the selective R-enantiomer of modafinil (which itself contains the R and S enantiomers), a total of almost three quarters of patients in the study

had been previously exposed to treatment the same as, or very similar to that used first line in UK practice.

c) Is there any evidence or clinical justification that previous treatment with modafinil would influence the effects of subsequent treatments, such as solriamfetol?

There is no evidence base or clinical justification to anticipate that any “hangover” effect of modafinil would exert an influence on subsequent treatment effects of solriamfetol, particularly not after a suitable washout period has been completed.

The study entry criteria excluded:

“Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline visit corresponding to at least 5 half-lives of the drug(s) [redacted]Examples of excluded medications include OTC [redacted] Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least 7 days prior to the Baseline visit, in the opinion of the Investigator.”

As such, modafinil was withdrawn a sufficient time in advance of the study start to ensure that patients would not experience any residual impact of prior treatment on their daytime sleepiness.

d) CS B.3.9.1 reports on a health economic model subgroup analysis by prior modafinil use. Please provide clinical effectiveness evidence (particularly Epworth Sleepiness Scale [ESS] outcomes) for this subgroup (we note that

prior modafinil use is not one of the pre-specified subgroup analyses reported in CS B.2.7)?

Figure 1. TONES 2 subgroup analysis: LS mean (SE) change in ESS scores from baseline to week 12 for patients with prior modafinil use (mITT Population)

Abbreviations: ESS, Epworth sleepiness scale; LS, least squares; SE, standard erorr; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

Figure 2. TONES 2 subgroup analysis: LS mean (SE) change in ESS scores from baseline to week 12 for patients without prior modafinil use (mITT Population)

Abbreviations: ESS, Epworth sleepiness scale; LS, least squares; SE, standard erorr; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
* p<0.05; † p<0.01; ‡ p≤0.001 vs placebo.

Table 1. TONES 2: mean (SD) ESS values for the subgroup of patients with and without prior modafinil use

	Prior modafinil use			No prior modafinil use		
	Placebo [redacted]	75 mg [redacted]	150 mg [redacted]	Placebo [redacted]	75 mg [redacted]	150 mg [redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A2. Please clarify whether the 150 mg solriamfetol dose is typically used in more severe patients. If so, how is severity defined and/or what are the criteria for use of the 150 mg solriamfetol dose?

The TONES studies were not designed to determine whether or not higher doses of solriamfetol were typically used for patients with more severe disease.

In TONES 2 patients were randomised and stratified according to baseline values of the efficacy endpoint, in to fixed dose treatment arms. The observed mean levels of ESS (and MWT) at baseline were very similar across all arms in the study. There was no option for investigators to select or titrate a patient's dose of solriamfetol based on the severity of their disease across the duration of the study.

During the titration phase of TONES 5, investigators were guided by the protocol to titrate patients up to the maximally tolerated dose, at a minimum of 3 day intervals. Titration was not based on objective measures of clinical benefit or response (such as change in ESS) specifically, nor on severity of disease, but rather on whether the dose was tolerated or not. The direction was to titrate patients to the maximally effective dose (300 mg) unless not tolerated.

As such, it is not possible from the TONES study data sets to determine whether or not solriamfetol 150 mg is typically used for more severe patients. ESS “severity” was also not defined in the TONES studies (beyond the requirement for a baseline ESS of ≥ 10), nor were any “criteria” defined for “use” of the 150 mg dose in relation to disease severity. This is consistent with UK clinical practice, as described in the KOL Clinical Practice Interviews, where ESS categorisation into mild, moderate or severe is not used in clinical practice and categorisation is therefore not clinically relevant.

Clinical experience in the US to date has been that approximately 50% of patients remain on the lowest dose (75 mg in the narcolepsy indication). There are no data from US practice to describe the distribution of doses by severity of a patient’s condition, nor the clinical criteria used to titrate up to 150 mg.

Advice from KOL Clinical Practice Interviews informs that, as is common practice in the UK, clinicians will titrate solriamfetol slowly, based on clinical effectiveness and tolerability, with the intention to maintain patients on the lowest effective and tolerated dose, rather than titrating to the highest tolerated one. This might reasonably support that most, if not all patients would be started on the lowest dose (as would be consistent with the license), to assess tolerability and response, regardless of the baseline severity of their ESS, before considering titration to 150 mg.

A3. CS Section B.1.3 states that cataplexy affects approximately 70% of patients with narcolepsy. In the TONES 2 RCT cataplexy was present in 50.8% of patients and in TONES 1 cataplexy was present in 35.5% of patients. Please comment whether there are any reasons why the proportion of participants with cataplexy in the company clinical trials are lower than that estimated for the general narcolepsy patient population.

There is no documented explanation for this apparent numerical difference in the proportion of patients included with cataplexy and narcolepsy, as compared to the general population estimate. Three potential explanations may, however, be worthy of consideration in this context.

First, the sample sizes are small and simple, random effects may explain some differences (for example, a small number of additional patients included with cataplexy would rapidly shift the proportionate balance).

Second, the difference may relate to an effect of the study design, which excluded continuation of anti-cataplexy treatments during the study. It is possible that some patients were less willing to stop their cataplexy treatment for the duration of the study, particularly when advised that it was possible that the investigational treatment most likely would not have an effect on treating their cataplexy. It is not inconceivable that this might understandably skew the relative willingness of patients to enter the study under these conditions.

Third and possibly most likely, a combination of both points above is relevant.

A4. CS B.2.4.3.3 describes which patients who entered the TONES 5 study. Please complete the following table to clarify the numbers of patients from different trials and with different underlying causes of excessive daytime sleepiness (i.e. narcolepsy or OSA).

Data were added to the table below.

	ADX-N05 201	TONES 1 (ADX-N05 202)	TONES 2	15-005	TONES 3	TONES 4	15-004
Indication	Narcolepsy				OSA		
Group A or B?	B	B	A	B	A	B	B
Screened for entry	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised into withdrawal phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Per-protocol population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Safety Population is defined as all subjects who received at least one dose of study medication in the open label phase. Randomized Population is defined as all subjects randomized into Withdrawal Period and received at least one dose of drug in that period. Modified Intent-To-Treat (mITT) Population is defined as subjects who were randomized in the Randomized Withdrawal Period, received at least one dose in that phase, and who have at least one evaluable efficacy data point at Week 29 (Group A) or Week 28 (Group B); Per Protocol Population is defined as mITT subjects who completed the 2-week Randomized Withdrawal Period according to protocol specifications without a major protocol violation.

Trial outcome measures

A5. Please provide a reference for the ESS questionnaire completed by patients with regard to the level of sleepiness they experienced over the [redacted] (including a reference for its validation for this duration).

The version of ESS used, with a [redacted] look back is a validated version of ESS. The Broderick 2013 publication cited below (1) (as referenced in TONES CSRs) examined the accuracy of responses on the Epworth Sleepiness Scale (ESS) across 3, 7, and 28-day reporting periods. Results showed that accuracy on recall was comparable regardless of the length of the reporting period: "Patients' accuracy on recall was comparable, regardless of the length of the reporting period from 3 days through a month."

Broderick, J. E., Junghaenel, D. U., Schneider, S., Pilosi, J. J., & Stone, A. A. (2013). Pittsburgh and Epworth sleep scale items: accuracy of ratings across different reporting periods. Behavioral sleep medicine, 11(3), 173-188.

A6. CS Table 6 states that the validity of the Work Productivity and Activity Impairment (WPAI) questionnaire has been established in a number of diseases. Has validity been established for narcolepsy or any other sleep disorder?

The WPAI was developed to measure the effect of health and symptom severity on work productivity and regular activities during the past 7 days. Construct validity and reproducibility of the instrument was established in a sample of 106 individuals who were employed and affected by *any health problem*, rather than a specific illness or set of symptoms (2). Since that time, the validity of the WPAI has been established in a large number of therapeutic areas (3-8), and the instrument has been shown to be responsive when determining treatment differences in a number of clinical trials (9-12). Of particular interest, the WPAI has successfully measured the impact of sleep disorders on work performance across therapeutic areas including OSA, narcolepsy, excessive sleep, insomnia, and psoriasis (13-17). The TONES studies used the WPAI-SHP v2.0, which has identical questions to the WPAI-GH, except that the question clarifies that the respondent is being asked to describe the impact of their sleep disorder on work performance and activities.

Trial subgroup analyses

A7. What was the clinical rationale for the three pre-planned subgroups analysed in the TONES 2 trial?

The three planned subgroups for TONES 2 were specified as follows:

- *Subgroup 1. The effect of solriamfetol by presence or absence of cataplexy.*
  There may be a theoretical potential that patients with narcolepsy and cataplexy might have differing amounts of EDS compared to those without cataplexy, or might theoretically respond differently to a wake-promoting treatment. Patients were therefore stratified in the randomisation process by the presence or absence of cataplexy, to ensure that any such theoretical differences would not introduce bias to the treatment arms through accidental imbalance. Analysis of this potential subgroup was also therefore specified, to confirm an absence of such effects due to the presence of cataplexy.

- *Subgroup 2. solriamfetol effect by region,*
  and *Subgroup 3. solriamfetol effect by country*
  These analyses were included in case of requirements by local regulatory authorities to provide data in specific country populations included in the study. There was no anticipation or a clinical rationale for an expected difference in response.

A8. Were any statistical interaction tests performed for the three subgroups analysed in the TONES 2 trial?

Tests of interaction were not carried out. They were not deemed necessary by regulators, due to the overall hierarchical structure of the statistical analysis plan.

A9. It is stated that the pre-planned subgroup analyses in the TONES 2 trial included region, and country, and it is also stated that CS page 85 that “For Europe ([redacted]), the analysis was limited by small sample size”. We note that subgroup analyses results do not appear to have been given in the CS by country. Please provide the countries included in the analyses and the subgroup analyses results for these countries.

Subgroup analyses by country were not conducted due to small numbers in all countries except the US (see Table 2).

Table 2. Patient numbers by country for TONES 2

Country	Placebo	75 mg	150 mg	300 mg (unlicensed)
USA	[redacted]	[redacted]	[redacted]	[redacted]
Canada	[redacted]	[redacted]	[redacted]	[redacted]
Finland	[redacted]	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]	[redacted]

A10. On CS page 85 in relation to the TONES 5 trial it is stated that "Demographics and clinical characteristics for subgroups were not defined". Please clarify the meaning of this statement.

Summary demographic and clinical characteristics for each subgroup were not generated as part of the subgroup analysis.

A11. The Clinical Study Report for TONES 2 references a statistical analysis plan (SAP) in Appendix 16.1.9. Documentation of Statistical Methods. This appendix does not appear to have been supplied to the ERG. Please provide this appendix.

This has been provided as a separate document: "CONFIDENTIAL. TONES 2 – 16.1.9 – Statistical Analysis Plan".

Trial results

A12. Clinical effectiveness results for the TONES 2 and TONES 1 trials are presented for modified ITT (mITT) populations (CS section 2.6.1 and 2.6.2).

a) Please justify the use of data from the mITT populations in the presentation of the clinical effectiveness results (CS Section B.2.6).

Use of the mITT population was pre-specified as the primary population for analysis in the regulatory and ethically approved clinical trial protocol.

Excluding patients from the ITT analysis who either did not take a dose of study drug, or did not have at least baseline and one post-baseline MWT or ESS measure, was deemed appropriate by regulatory and ethics reviewers.

Use of mITT for analysis of effectiveness is a widely accepted statistical and regulatory approach to manage the small population of patients who either never take treatment, or have insufficient evaluable data, after randomisation. In reality, only [redacted] (out of 179) in total, across the placebo, 75 mg and 150 mg arms, were excluded from the ITT analysis for these reasons.

It should also be noted that the analyses for TONES 1 were ITT rather than mITT.

b) Sensitivity analyses were conducted to assess the impact of missing data. Did these sensitivity analyses include data for the participants who did not meet the criteria for the mITT populations?

No sensitivity analyses to assess the impact of missing data were carried out in the mITT population for TONES 2. Sensitivity analyses would not have been relevant for TONES 1, as analysis used the ITT Population.

A13. Please report the TONES 2 ITT mean (n and SD) change from baseline ESS scores by treatment arm and at each time point 1, 4, 8 and 12 weeks (as in CS Figure 4).

Due to the quantity of clarification requested and the resource limitations within Jazz (as previously described), the focus of responses has been on ERG Priority questions and those other questions where we believe clarification is most relevant. As such, this question has not been fully answered, however given that there is a very small difference in population size ([redacted]) between the ITT and mITT populations, we do not believe there would be any relevant impact of this marginal difference on the efficacy outcomes in the trial.

A14. Please report the TONES 2 ITT mean (n and SD) change from baseline EQ-5D-5L Index scores for each treatment arm and each time point (1, 4, 8 and 12 weeks) using a graph similar to Figure 4.

Due to the quantity of clarification requested and the resource limitations within Jazz (as previously described), the focus of responses has been on ERG Priority

questions and those other questions where we believe clarification is most relevant. As such, this question has not been fully answered, however given that there is a very small difference in population size ([redacted]) between the ITT and mITT populations, we do not believe there would be a relevant impact of this marginal difference on the efficacy outcomes in the trial.

A15. Please report the numbers of patients from the TONES 5 study contributing results to each of the groups in CS Table 17 (Group A 75 mg; Group A 150 mg, Group B 75 mg, Group B 150 mg).

Patient numbers for each group have been added to the header row below:

Table 17. 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 [redacted]	150 mg [redacted]	75 mg [redacted]	150 mg [redacted]
Change from baseline† at week 2	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline† at week 40	[redacted]	[redacted]	NA	NA
Change from baseline† at week 52	NA	NA	[redacted]	[redacted]

Abbreviations: NA, not applicable; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness. Data presented as mean (SD).
† Baseline defined as the baseline of the parent study for Group A and baseline of TONES 5 for Group B.

A16. Please report the TONES 5 mean (n and SD) ESS scores for Group A and B at each time point 0, 1, 4, 8 and 12 weeks (as in CS Figure 7 and 8).

Data at the timepoints listed above are not available for TONES 5. As agreed during the ERG clarification call on 5th February 2020, the data requested have been presented below for the timepoints that were assessed in TONES 5. These data are presented in figure/plot format in CS Figure 7 and 8, respectively.

Table 3. TONES 5: mean (SD) ESS score for patients with narcolepsy in Group A during the open-label phase (Safety Population)

	Mean	SD
Baseline of the parent study ([redacted])	17.3	[redacted]
Last assessment of parent study ([redacted])	13.2	[redacted]
Week 2 ([redacted])	10.0	[redacted]

Week 14 ([redacted])	10.5	[redacted]
Week 27 ([redacted])	11.1	[redacted]
Week 40 ([redacted])	11.4	[redacted]

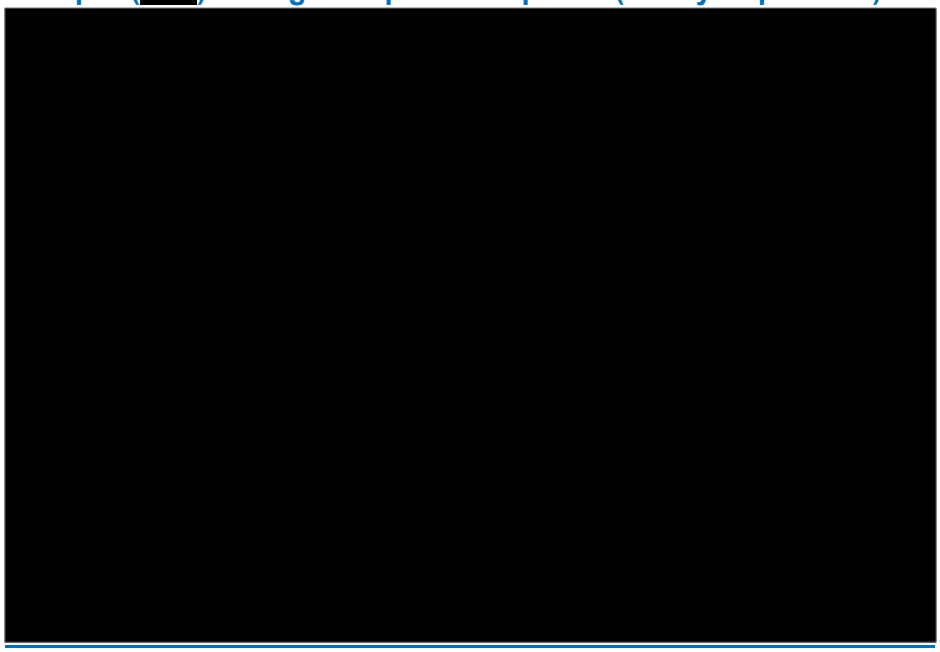
Table 4. TONES 5: mean (SD) ESS score for patients with narcolepsy in Group B during the open-label phase (Safety Population)

	Mean	SD
Baseline of TONES 5 ([redacted])	17.9	[redacted]
Week 2 ([redacted])	10.2	[redacted]
Week 14 ([redacted])	9.9	[redacted]
Week 26 ([redacted])	10.2	[redacted]
Week 39 ([redacted])	10.6	[redacted]
Week 52 ([redacted])	10.3	[redacted]

A17. Please report the TONES 5 mean (n and SD) EQ-5D-5L Index scores for Group A and B at each time point (0, 1, 4, 8 and 12 weeks) using a graph similar to Figures 7 and 8.

As above, these timepoints are not available for TONES 5, and as agreed during the clarification call on 5th February 2020, the data are instead presented below for the timepoints that were assessed in TONES 5, in both table and figure/plot format.

Figure 3. TONES 5: mean (SD) EQ-5D-5L Index score for patients with narcolepsy in Group A ([redacted]) during the open-label phase (Safety Population)



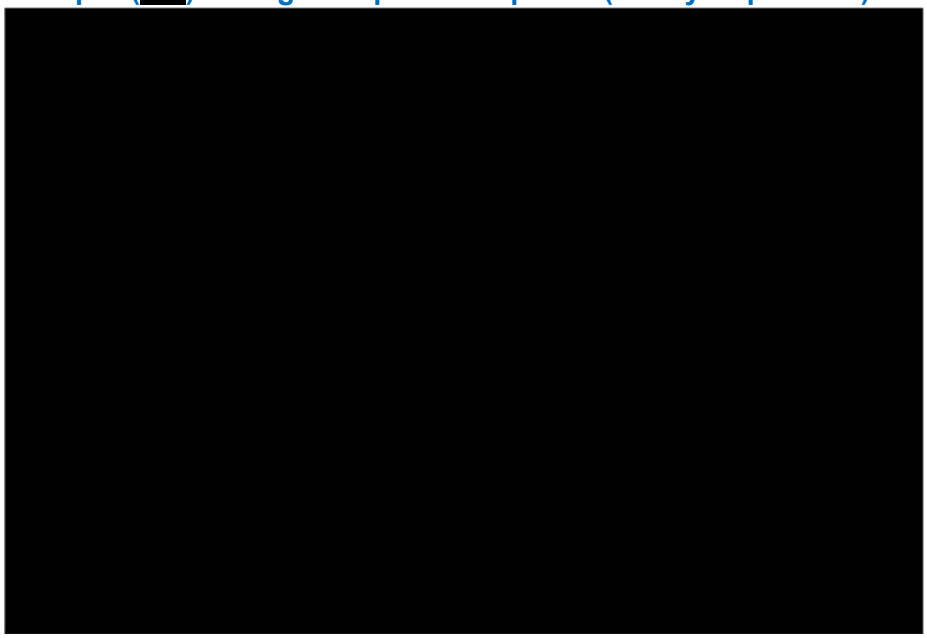
Abbreviations: CSR, clinical study report; EQ-5D-5L, 5-level EQ-5D version; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: CSR Table 14.2.9.1a (18).

Table 5. TONES 5: mean (SD) EQ-5D-5L Index score for patients with narcolepsy in Group A during the open-label phase (Safety Population)

	Mean	SD
Baseline of the parent study ([redacted])	[redacted]	[redacted]
Last assessment of parent study ([redacted])	[redacted]	[redacted]
Week 14 ([redacted])	[redacted]	[redacted]
Week 27 ([redacted])	[redacted]	[redacted]
Week 40 ([redacted])	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; EQ-5D-5L, 5-level EQ-5D version; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: CSR Table 14.2.9.1a (18).

Figure 4. TONES 5: mean (SD) EQ-5D-5L Index score for patients with narcolepsy in Group B ([redacted]) during the open-label phase (Safety Population)



Abbreviations: CSR, clinical study report; EQ-5D-5L, 5-level EQ-5D version; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: CSR Table 14.2.9.1a (18).

Table 6. TONES 5: mean (SD) ESS score for patients with narcolepsy in Group B (n=40) during the open-label phase (Safety Population)

	Mean	SD
Baseline of TONES 5 ([redacted])	[redacted]	[redacted]
Week 14 ([redacted])	[redacted]	[redacted]
Week 26 ([redacted])	[redacted]	[redacted]
Week 39 ([redacted])	[redacted]	[redacted]
Week 52 ([redacted])	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; EQ-5D-5L, 5-level EQ-5D version; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: CSR Table 14.2.9.1a (18).

Indirect treatment comparison

A18. Priority question: The search strategy does not appear to have picked up all the modafinil and pitolisant RCTs (CS Appendix D.1.3.3, Table 4) identified from the previous meta-analyses identified in the CS (Golicki, 2010;(19) Lehert, 2018(20)). The following studies are not listed in either the company's included or excluded studies list:

Modafinil studies:

- Billiard M, Besset A, Montplaisir J et al: Modafinil: a double-blind multicentric study. Sleep, 1994; 17: S107–12
- Boivin DB, Montplaisir J, Petit D et al: Effects of modafinil on symptomatology of human narcolepsy. Clin Neuropharmacol, 1993; 16: 46–53
- Broughton RJ, Fleming JA, George CF et al: Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology, 1997; 49: 444–51
- Saletu MT, Anderer P, Saletu-Zyhlarz GM et al: EEG-mapping differences between narcolepsy patients and controls and subsequent double blind, placebo-controlled studies with modafinil. Eur Arch Psychiatry Clin Neurosci, 2005; 255: 20–32

Pitolisant study:

- Kollb-Sielecka M, et al. The European medicines agency review of pitolisant for treatment of narcolepsy: summary of the scientific assessment by the Committee for Medicinal Products for Human Use. Sleep Med. 2017;33:125–129.

Please indicate whether these studies were considered for the company's own systematic review. If the studies were considered and excluded, please provide the reason for their exclusion (see also question A21).

All 5 trials listed above were identified in the SLR search. The respective reasons for exclusion are listed below (Table 7).

Table 7. Exclusion Reasons for Citations from Previous Meta-Analyses

Citation	Rationale for exclusion
Billiard, 1994:	Crossover study, does not report data at first cross
Boivin, 1993	Only 10 patients total, so excluded because even if reported, data at first cross would include only 5 patients
Broughton, 1997	Crossover study, does not report data at first cross
Saletu, 2005	Crossover study, does not report data at first cross
Kollb-Sielecka, 2017	This is a review of the pivotal trials for pitolisant (Dauvilliers, 2013; Szakacs, 2017). There is a third trial for pitolisant, HARMONY Ibis, which was not published but is described in Kollb-Sielecka, 2017. According to the NICE evidence review for pitolisant, "The EPAR states that HARMONY Ibis was most likely underpowered, and the low dose may not have been sufficient for many people. In HARMONY I, 61% of participants were taking pitolisant 40 mg per day during the stable dose phase of the trial." (https://www.nice.org.uk/advice/es8/chapter/evidence-review) For the HARMONY Ibis study, Kollb-Sielecka does provide the change in ESS and MWT from baseline to final visit for each trial arm. However, it does not provide 1) full inclusion criteria, 2) patient characteristics, 3) concurrent medication use per arm, 4) patient number per arm, and 5) baseline ESS and MWT. Without this information, it is not possible to determine whether HARMONY Ibis is sufficiently similar for comparison or the relative treatment effect of the variable-dose pitolisant on ESS and MWT. Other outcomes listed in Lehert, 2018 for HARMONY Ibis that are of interest to this ITC include CGI-C and adverse events; these are not provided anywhere in Kollb-Sielecka, 2017. Dr Lehert is a member of the HARMONY study group and may have used HARMONY Ibis data not available publicly for the ITC performed in the Lehert, 2018 publication.

A19. Priority question: Please provide calculations for the imputed values for the ESS outcomes (CS Section D.1.5.1, Table 9).

Table 8. Change from baseline, ESS outcomes

Trial	Timepoint (week)	Treatment (qd)	N	Mean	SE	Notes	Imputation Calculation
ESS change from baseline at 4 weeks							
TONES 2	4	Placebo	54	-2.200	0.590	-	-
		Solriamfetol 75 mg	52	-3.300	0.590		
		Solriamfetol 150 mg	53	-5.600	0.600		
TONES 1	4	Placebo	47	-2.405	0.688	Mean change and SE digitized from publication figure	-
		Solriamfetol 150 mg	43	-5.569	0.802	Dose labelled as 150 mg for 4-week timepoint	-
Dauvilliers, 2013	3	Placebo	30	-3.000	0.537	Mean change (geometric) and SE calculated using 0 and 3 week means and SE* Timepoint standardised to 4 week	$\frac{\sqrt{[2.5^2 + 4.3^2 + (2 * 0.55 * 2.5 * 4.3)^2]}}{\sqrt{30}}$
		Pitolisant ≤40 mg	31	-5.800	0.915		$\frac{\sqrt{[6.0^2 + 2.5^2 + (2 * 0.55 * 6.0 * 2.5)^2]}}{\sqrt{31}}$

Trial	Timepoint (week)	Treatment (qd)	N	Mean	SE	Notes	Imputation Calculation
Xyrem, 2002	4	Placebo	34	-1.919	0.494	Mean change calculated from medians at 0 and 4 wk† SE imputed from placebo values‡	$\frac{[(0.590 * 54) + (0.688 * 47) + (0.537 * 30)]}{(54 + 47 + 30)}$
		Sodium oxybate 3 g	34	-0.907	0.555	Mean change calculated from medians at 0 and 4 wk† SE imputed from available values‡	$\frac{[(0.590 * 54) + (0.590 * 52) + (0.600 * 53) + (0.688 * 47) + (0.802 * 43) + (0.537 * 30) + (0.915 * 31)]}{(54 + 52 + 53 + 47 + 43 + 30 + 31)}$
		Sodium oxybate 6 g	33	-2.997	0.555		
		Sodium oxybate 9 g	35	-4.952	0.555		
Xyrem, 2005	4	Placebo	57	-1.500	0.494	Mean change calculated from medians at 0 and 4 wk† SE imputed from placebo values‡	$\frac{[(0.590 * 54) + (0.688 * 47) + (0.537 * 30)]}{(54 + 47 + 30)}$
		Sodium oxybate 4.5 g	63	-1.000	0.555	Mean change calculated from medians at 0 and 4 wk† SE imputed from available values‡	$\frac{[(0.590 * 54) + (0.590 * 52) + (0.600 * 53) + (0.688 * 47) + (0.802 * 43) + (0.537 * 30) + (0.915 * 31)]}{(54 + 52 + 53 + 47 + 43 + 30 + 31)}$
		Sodium oxybate 6 g	54	-3.000	0.555		
		Sodium oxybate 9 g	41	-6.000	0.555		

Trial	Timepoint (week)	Treatment (qd)	N	Mean	SE	Notes	Imputation Calculation
Black, 2006	4	Placebo	53	1.000	0.494	Mean change calculated from medians at 0 and 4 wk[†] SE imputed from placebo values[‡]	$\frac{[(0.590 * 54) + (0.688 * 47) + (0.537 * 30)]}{(54 + 47 + 30)}$
		Sodium oxybate 6 g	48	-2.000	0.555	Mean change calculated from medians at 0 and 4 wk[†] SE imputed from available values[‡] Dose labelled as 6 g for 4-week timepoint	$\frac{[(0.590 * 54) + (0.590 * 52) + (0.600 * 53) + (0.688 * 47) + (0.802 * 43) + (0.537 * 30) + (0.915 * 31)]}{(54 + 52 + 53 + 47 + 43 + 30 + 31)}$
ESS change from baseline at 8 weeks							
TONES 2	8	Placebo	53	-2.100	0.630	-	-
		Solriamfetol 75 mg	49	-3.400	0.640		
		Solriamfetol 150 mg	52	-5.200	0.640		
Dauvilliers, 2013	8	Placebo	25	-3.400	0.840	SE calculated from reported SD and N	-
		Pitolisant ≤40 mg	26	-5.800	1.216		-
Szakacs, 2017	7	Placebo	51	-1.900	0.528	Imputed placebo SE[‡] Timepoint standardised to 8 week	$\frac{[(0.630 * 53) + (0.840 * 25)]}{(53 + 25)}$
		Pitolisant ≤40 mg	54	-5.400	0.583	Imputed available SE	$\frac{[(0.630 * 53) + (0.640 * 49) + (0.640 * 52) + (0.840 * 25) + (1.216 * 26)]}{(53 + 49 + 52 + 25 + 26)}$

Trial	Timepoint (week)	Treatment (qd)	N	Mean	SE	Notes	Imputation Calculation
Xyrem, 2005	8	Placebo	58	-0.500	0.528	Mean change calculated from medians at 0 and 8 wk† SE imputed from placebo values‡	$\frac{[(0.630 * 53) + (0.840 * 25)]}{(53 + 25)}$
		Sodium oxybate 4.5 g	61	-1.000	0.583	Mean change calculated from medians at 0 and 8 wk† SE imputed from available values‡	$\frac{[(0.630 * 53) + (0.640 * 49) + (0.640 * 52) + (0.840 * 25) + (1.216 * 26)]}{(53 + 49 + 52 + 25 + 26)}$
		Sodium oxybate 6 g	55	-2.000	0.583		
		Sodium oxybate 9 g	43	-5.000	0.583		
Black, 2006	8	Placebo	53	0.000	0.528	Mean change calculated from medians at 0 and 8 wk† SE imputed from available values‡	$\frac{[(0.630 * 53) + (0.840 * 25)]}{(53 + 25)}$
		Sodium oxybate 9 g	49	-3.000	0.583	Mean change calculated from medians at 0 and 8 wk† SE imputed from available values‡ Dose labelled as 9 g for 8-week timepoint	$\frac{[(0.630 * 53) + (0.640 * 49) + (0.640 * 52) + (0.840 * 25) + (1.216 * 26)]}{(53 + 49 + 52 + 25 + 26)}$

Abbreviations: ESS, Epworth Sleepiness Scale; qd, once daily; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
* Imputation of SE performed as described by the Agency for Healthcare Research and Quality.(21).
† Use of medians as means performed as described by Hozo, 2005.(22)
‡ Imputation of SE performed as described by the Cochrane Collaboration.(23)

A20. An assessment of inconsistency is ruled out due to “a lack of closed loops of evidence”. However, there are closed loops e.g. between the sodium oxybate studies where it is possible to examine inconsistency. Please conduct this assessment.

Consistency analysis is not possible on other outcomes due to lack of closed loops (the closed loops shown in the network diagrams are due to single multi-arm trials and therefore cannot be analysed for inconsistency). Consistency evaluation was feasible only for ESS and discontinuations due to AEs; results are summarised below.

Inconsistency

Inconsistency models were run for all feasible outcomes, which include ESS week 4 (Figure 5) and week 8 (Figure 6) as well as discontinuations due to AEs (Figure 7). Closed loops in all other outcomes are due to multi-arm trials and therefore are unable to be analysed for inconsistency. Inconsistency results are depicted as the residual deviance contribution in the base case model compared to the inconsistency model for each study. Consistent outcomes will have similar residual deviances in the base case and inconsistency models and therefore appear along a diagonal line. Studies which are inconsistent will appear far from the diagonal line. Inconsistency analysis yielded highly consistent results across all studies and analysed outcomes. This is likely due to the small number of studies included in the analyses, leaving little potential room for inconsistency.

Figure 5. ESS Week 4 Inconsistency Results

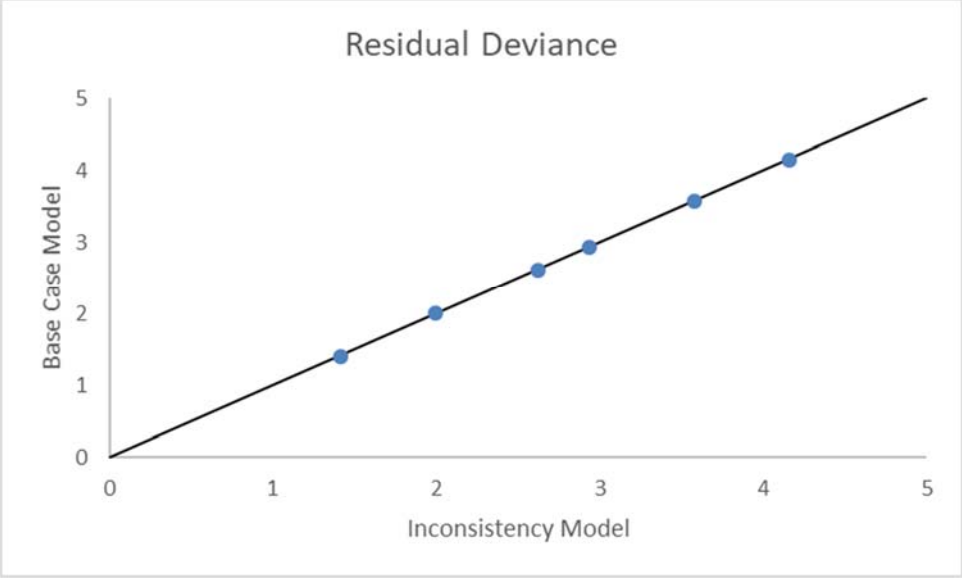


Figure 6. ESS Week 8 Inconsistency Results

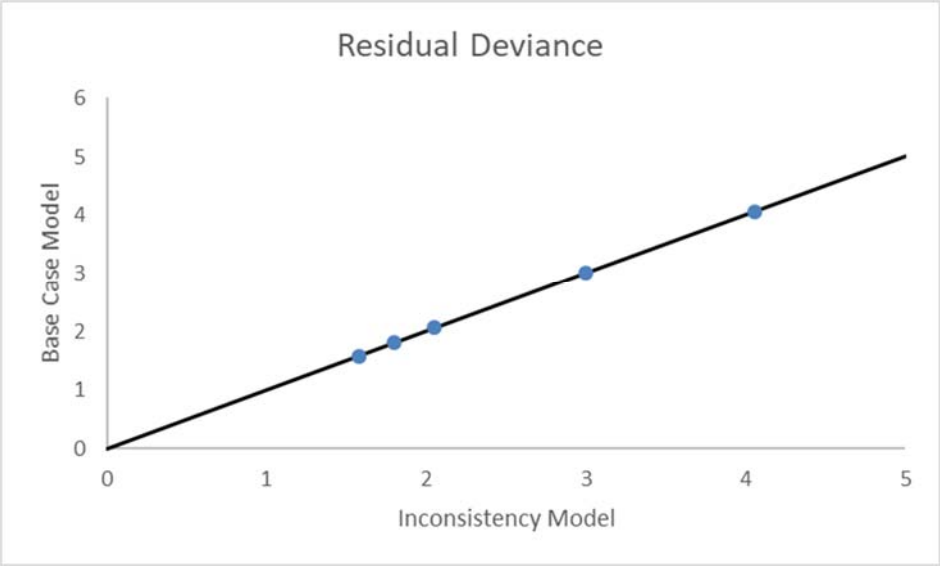
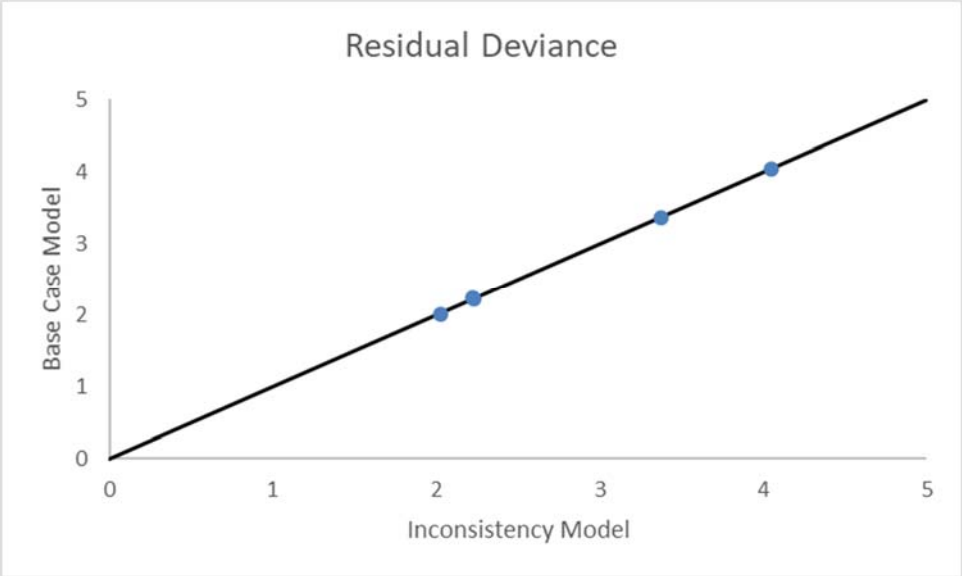


Figure 7. Discontinuations Due to AEs Inconsistency Results



A21. Priority question: CS Appendix D Table 3 lists the studies included in the ITC. The Dauvilliers 2013 pitolisant RCT (24) and the Black 2006 sodium oxybate RCT (25) both included modafinil treatment arms that were not included in the ITC network.

a) Given that Appendix D section D.1.3.1 states that one of the reasons modafinil was included as a comparator for the SLR was in case a modafinil trial might add strength to the network. Please explain why the modafinil treatment arms of Dauvilliers 2013 (24) and Black 2006 (25) were excluded.

As reported in Form B section B.2.9.4 under “dose labeling”, modafinil itself is not considered a comparator in the ITC. The variable dose modafinil arms in Dauvilliers, 2013 and Black, 2006 were different (i.e., 100-400 mg once daily cannot necessarily be compared with 200-600 mg once daily, particularly since mean or median doses used are not provided by these publications). Since these arms are not identical, their inclusion would have no effect on network strength.

b) The inclusion of the modafinil studies and arms (from Black & Dauvilliers) would also have added connectivity to the network. Is there evidence of a dose effect for modafinil or can different doses be combined? Please add the modafinil arms of studies included in the ITC to the network and present updated results. Please also add any modafinil/other relevant arms from trials identified from the previous meta-analyses by Golicki, 2010;(19) and Lehert, 2018(20) to the ITC.

There is evidence of a dose effect of modafinil for some outcomes, this can be found in the pivotal trials for modafinil in narcolepsy (Table 9). Statistical analyses were not performed by the study authors to determine whether the differences in 200 and 400 mg modafinil outcomes were statistically significant, but there is a numerical difference in ESS and CGI-C. Therefore, we do not believe it is appropriate to include the modafinil arms from Dauvillers, 2013 and Black, 2006 in the ITC, particularly since the actual mean/median dose used is not known.

Table 9. Change from Baseline in ESS, MWT20, and CGI-C

	US Modafinil, 1998			US Modafinil, 2000		
	Placebo	200 mg	400 mg	Placebo	200 mg	400 mg
ESS, mean (SE)	-1.2 (0.3)	-3.5 (0.5)	-4.1 (0.5)	-1.8 (0.3)	-4.4 (0.5)	-5.7 (0.5)
MWT 20, mean (SE)	-0.7 (0.3)	2.3 (0.5)	2.3 (0.6)	-0.5 (0.4)	2.1 (0.6)	1.9 (0.5)
CGI-c, %	37	64	73	38	58	61

Abbreviations: CGI-c, clinician global impression of change; ESS, Epworth Sleepiness Scale; MWT20, 20 minute maintenance of wakefulness test; SE, standard error.
Source: US Modafinil 1998 and 2000 (26, 27).

A22. Section D.1.4.2 refers to eligibility criteria for RCTs to be included in the analysis of had to have at least 10 patients in each arm. Were any studies excluded on this basis?

As indicated in the PRISMA, 6 studies were excluded for having fewer than 10 patients per arm. However, all these studies would have been excluded for additional reasons that could be identified at the title/abstract level (Table 10).

Table 10. Citations Excluded Due to < 10 Patients Per Arm and Additional Reasons

Citation	Other reason for exclusion
Alshaikh, 2011	Study design not of interest: case series/case report
Arnulf, 1997	Population not of interest: obstructive sleep apnoea
Baier, 2011	Comparator not of interest: hypocretin-1 (orexin A) versus placebo
Bittencourt, 2008	Population not of interest: obstructive sleep apnoea
Donjacour, 2011	< 2 week duration
Wyler, 1975	Comparator not of interest: methysergide

A23. Priority question: CS Appendix D section D.1.5.1 states “No apparent or potential differences in the underlying disease of patient populations was identified”, however no evidence to support this statement is presented. Please provide information about the patients enrolled in each study included in the NMA. For example, how was narcolepsy defined and/or confirmed (narcolepsy classification critieria, sleep latency tests, ESS score for inclusion, number of cataplexy events etc).

	TONES 2			TONES 1		Dauvilliers, 2013			Szakacs, 2017		Xyrem, 2002				Xyrem, 2005				Black, 2006	
	Placebo	Solriamfetol 75 mg qd	Solriamfetol 150 mg qd	Placebo	Solriamfetol 150 / 300 mg qd	Placebo	Pitolisant 10-40 mg qd	Modafinil 100-400 mg qd	Placebo	Pitolisant 5-40 mg qd	Placebo	Sodium oxybate 3 g qd	Sodium oxybate 6 g qd	Sodium oxybate 9 g qd	Placebo	Sodium oxybate 4.5 g bd	Sodium oxybate 6 g bd	Sodium oxybate 9 g bd	Placebo	Sodium oxybate 6-9 g qd
Narcolepsy definition	Diagnosis of narcolepsy type 1 or 2 according to criteria in either the ICSD, 3rd edition or DSM, 5th edition			Diagnosis of narcolepsy type 1 or 2 according to the ICSD, 2nd edition		Diagnosis of narcolepsy with or without cataplexy according to ICSD, 2nd edition			Diagnosis of narcolepsy with cataplexy according to ICSD, 2nd edition		Diagnosis of narcolepsy according to American Sleep Disorders association				Prior diagnosis of narcolepsy based on overnight PSG and MSLT within previous 5 years; current narcolepsy symptoms including EDS, cataplexy, and sleep attacks ~daily for ≥3 months				Diagnosis of narcolepsy according to criteria in the ICSD	
Cataplexy as inclusion	No			No		No			Yes. ≥3 cataplexies/wk		No				Yes				No	
Cataplexy, %	59	59	59	49	44	80	81	82	100	100	100	100	100	100	100	100	100	100	58	28
Cataplexy attacks per week, mean	NR			NR		6.4	8.4	7.7	9.2	11	NR				18.91	37.95	26.52	25.59	NR	
Cataplexy attacks per week, median	NR			NR		NR			NR		21				14.96	16.00	17.00	18.00	NR	
Sleep latency for inclusion	Baseline mean sleep latency <25 mins in MWT40			Baseline mean sleep latency <10 mins in MWT40		PSG and baseline mean sleep latency ≤8 mins with ≥2 sleep onset REM periods, done within previous 5 years			PSG and MSLT with ≥2 sleep onset REM periods, done within previous 1 year		NR				NR				NR	
MWT20	5.6	7.1	7.2	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	NR	NR	NR
ESS for inclusion	BL ESS ≥10			BL ESS ≥10		BL ESS ≥14			BL ESS ≥12		NR				NR				NR	
ESS, mean	17.3	17.3	17.0	17.4	17.3	18.9	17.8	18.5	17.4	17.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ESS, median	17.0	18.0	17.0	NR	NR	NR	NR	NR	NR	NR	19.0	17.0	17.6	17.1	17.5	18.0	19.0	19.0	16.0	15.0

Abbreviations: BL, baseline; DSM, Diagnostic and Statistical Manual of Mental Disorders; EDS, Excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; ICSD, International Classification of Sleep Disorders; MSLT, multiple sleep latency test; MWT, Maintenance of wakefulness test; NR, not reported; PSG, Polysomnography; REM, rapid eye movement; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

A24. Priority question: Please provide justification for the use of the solriamfetol individual patient data (IPD) to calculate comparator response in the economic model.

The primary end-point in TONES 2 and in other studies identified within the NMA only report the mean change in ESS from baseline. While this demonstrates the effectiveness across the whole cohort, for a short period (typically 8 to 12 weeks), it is assumed that some patients will respond more than others and some will not respond at all, and as such the mean change from baseline cannot be directly used to reflect treatment beyond the trial. By utilising the IPD we have attempted to quantify the proportion of patients that would be considered responders in clinical practice (those with a ≥ 3 unit improvement in ESS from baseline) and would continue therapy, from those that would be considered non-responders and subsequently stop taking treatment.

a) Please state whether there is any precedent for using this methodology.

We're not aware of a precedent for the methodology of utilising IPD to determine response however, as per question A24, although use of mean change from baseline demonstrates the effectiveness across the whole cohort, for a short period (typically 8 to 12 weeks), it is assumed that some patients will respond more than others and some will not respond at all; as such, the mean change from baseline cannot be directly used to reflect treatment beyond the trial. By utilising the IPD we have attempted to quantify the proportion of patients that would be considered responders in UK clinical practice (those with a ≥ 3 unit improvement in ESS from baseline) who would therefore continue therapy, from those that would be considered non-responders and who would subsequently stop taking treatment, for both solriamfetol and the comparators. Given the limited efficacy data available for the comparators, Jazz believe this is a suitable approach to most accurately reflect clinical treatment decisions beyond 12 weeks.

b) Please also clarify whether you are applying the mean change from baseline (relative to solriamfetol 150mg) to each IPD patient or if you are assigning a (normal?) distribution to the mean and 95% CrI and applying a random draw to each IPD patient?

The model applies the same mean change from baseline, relative to solriamfetol 150 mg, to each synthesised patient (i.e. for each comparator, the same mean change in ESS, relative to solriamfetol 150 mg, is applied to each IPD to generate the pseudo-IPD). Table 11 shows an illustrative example of pseudo-IPD generated for a comparator that has a mean change in baseline ESS, relative to solriamfetol 150 mg of -1 (that is that the mean change is one less than that achieved with solriamfetol 150 mg).

Table 11: Illustrative example of generating pseudo-IPD for a comparator

Patient ID	Solriamfetol 150 mg Change from baseline	Comparator, Change from baseline	Change in baseline relative to solriamfetol 150 mg
1	-3	-2	-1
2	-15	-14	-1
3	-1	0	-1

In PSA, for each PSA iteration, the mean change from baseline relative to solriamfetol 150 mg is sampled using a normal distribution and this figure is applied to all bootstrapped pseudo-IPD patients generated within the PSA simulation.

c) Use of the 150mg IPD assumes these patients are typical of a UK population, can you provide evidence to support this?

The use of the TONES 2 IPD with the exclusion of patients with ESS = 10 at baseline (who in UK clinical practice would not be considered to have EDS) was assumed to represent the UK population of patients with narcolepsy (i.e. those with a narcolepsy diagnosis and EDS defined as ESS >10). As described in the company submission, data on the clinical and demographic characteristics of patients with narcolepsy in the UK are extremely limited, and the available studies are approximately 20 years old or more, thus have questionable relevance to the current narcolepsy population. There is therefore no evidence to demonstrate whether or not the 150 mg IPD are typical of the UK population.

A25. Please explain why you chose the 150mg arm rather than the 75mg arm for the IPD. Did you conduct a scenario analysis using the 75mg arm from TONES 2 IPD, how did this impact the results?

The 150 mg arm was arbitrarily picked as the reference point for the ITC and as such the 150 mg IPD was as the reference point. The ITC has been re-run using the 75 mg as the reference arm; the mean change in ESS relative to 75 mg is presented in Table 12.

Table 12: Mean change in ESS relative to solriamfetol 75 mg

Product, daily dose	Mean ΔESS relative to solriamfetol 75 mg at week 8 (95% CrI)[a]
Solriamfetol, 75 mg	Reference product
Solriamfetol, 150 mg	1.80 (0.14, 3.46)*
Pitolisant (≤40 mg)	1.85 (-0.47, 4.18)
Sodium oxybate, 4.5 g	-1.15 (-3.65, 1.36)
Sodium oxybate, 6.0 g	-0.15 (-2.64, 2.34)
Sodium oxybate, 9.0 g	2.45 (0.29, 4.63)*

Abbreviations: CrI, credible interval; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness scale; IPD, individual patient data.
Δ represents change in ESS from baseline.
* Change compared to solriamfetol 75 mg (CrI did not cross 0).
†All patients, irrespective of response/non-response; ‡Change estimated via IPD.
a. With regards to the mean change in ESS relative to solriamfetol 150 mg; a negative figure means that the comparator is less effective than solriamfetol 150 mg with comparative efficacy reducing as this figure moves further from zero. Conversely, a positive figure means that the comparator is more effective than solriamfetol 150 mg with the comparative efficacy increasing as the figure moves further from zero.
b. With regards to the absolute change in ESS from baseline; Patients with EDS will have a high ESS as symptoms improve the ESS will reduce, as such a negative figure demonstrates the improvement in a patient's symptoms. As the figure moves further from zero the less EDS a patient will experience.

A scenario analysis utilising the 75 mg IPD from TONES 2 and generation of pseudo-IPD using the mean change in ESS relative to solriamfetol 75 mg (as defined in Table 12) was performed and the results are presented in Table 13 and Table 14.

Table 13. Results using the 75 mg IPD as the reference point – By dose

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£5,869 (£5,864 - £5,875)	13.374 (13.372 - 13.376)	42.887 (42.874 - 42.899)				
Solriamfetol 150mg	£9,745 (£9,738 - £9,752)	13.425 (13.423 - 13.427)	42.887 (42.874 - 42.899)	£3,876	0.050	£77,058	£77,058
Sodium Oxybate 4.5g	£9,814 (£9,801 - £9,828)	13.287 (13.284 - 13.289)	42.887 (42.874 - 42.899)	£69	-0.138	Dominated	Dominated
Sodium Oxybate 6g	£18,033 (£18,014 - £18,051)	13.337 (13.335 - 13.339)	42.887 (42.874 - 42.899)	£8,218	0.050	£163,340	Dominated
Pitolisant ≤40mg	£19,004 (£18,991 - £19,017)	13.425 (13.423 - 13.427)	42.887 (42.874 - 42.899)	£971	0.088	£11,011	Extendedly dominated
Sodium Oxybate 9g	£46,833 (£46,807 - £46,858)	13.475 (13.473 - 13.477)	42.887 (42.874 - 42.899)	£27,829	0.050	£560,902	£408,309

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. * South-West Quadrant of cost-effectiveness plane

Table 14. Results using the 75 mg IPD as the reference point – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£7,807	13.400	43.005			
Pitolisant	£19,004	13.425	43.005	£11,197	0.026	£438,026
Sodium oxybate	£24,893	13.366	43.005	£5,889	-0.059	Dominated

There are small differences in absolute costs and QALYs due to the variation in baseline characteristics between the 75 mg and 150 mg IPD data. However, the overall results are highly congruent to the original base case results demonstrating that solriamfetol is cost-effective when compared to pitolisant and sodium oxybate.

A26. Since TONES 1 150mg patients are included in the NMA, why are the same patients not also included in the IPD analysis of response which is confined to those patients in TONES 2?

The inclusion of the TONES 1 150 mg data in the IPD analysis of response was not feasible due to the length of time patients were treated with solriamfetol 150 mg in the study; patients only received 150 mg for the first 4 weeks of the trial, before being titrated up to the unlicensed 300 mg dose. As 150 mg was not used for longer time periods, the data could not be incorporated into the CEM.

A27. Please summarise the evidence that cataplexy and concomitant medication are treatment effect modifiers. Was this established through a review of the literature, or through soliciting expert opinion on key prognostic factors for narcolepsy and key treatment effect modifiers? How was any information on these used in the assessment of clinical heterogeneity in the ITC?

Evidence that cataplexy and related use of concomitant medication as a potential treatment effect modifier was established by internal expert opinion. No information was gathered from UK Clinical Expert opinion which contradicted this view. This information was used in a scenario analysis for sodium oxybate including the only study that did not include concomitant therapies, as discussed in CS B.2.9.5 “Impact of concomitant therapy”.

A28. In CS Appendix D Table 17 some of the baseline characteristics for the TONES 1 study do not match the values for the same characteristics presented in CS B.2.3.2.2 Table 9. Please check and correct Appendix D Table 17 as required.

Correct. There was a discrepancy for % male, Caucasian and mean BMI. These have been corrected in the table below (see blue text).

Table 15. Baseline characteristics of included trials assessing solriamfetol

	TONES 2			TONES 1	
Treatment arm	**Placebo**	**Solriamfetol 75 mg qd**	**Solriamfetol 150 mg qd**	**Placebo**	**Solriamfetol 150 / 300 mg qd**
N	59	59	59	49	44
Cataplexy, %	49	53	51	33	39
Age, mean, y	36	36.5	38.1	36.7	41
Age, median, y	32	36	38	NR	NR
Age range, y	18-70	18-68	20-68	NR	NR
Males, %	41	37	29	38.8	31.8
Caucasian, %	80	78	81	79.6	68.2
BMI, mean, kg/m^2	29.1	27.9	27.9	26.4	26.8
ESS, mean	17.3	17.3	17.0	17.4	17.3
ESS, median	17.0	18.0	17.0	NR	NR
MWT20	5.6	7.1	7.2	NR	NR
MWT40	6.2	7.5	7.9	5.7	5.7
CGI-s, mean†	NA	NA	NA	[redacted]	[redacted]
Baseline CGI-s, n (%)					
Normal	0	0	0	NR	NR
Borderline ill	0	0	0	NR	NR
Mildly ill	1 (1.7)	3 (5.1)	3 (5.1)	NR	NR
Moderately ill	14 (23.7)	14 (23.7)	16 (27.1)	NR	NR
Markedly ill	26 (44.1)	20 (33.9)	24 (40.7)	NR	NR
Severely ill	13 (22.0)	17 (28.8)	13 (22.0)	NR	NR
Among the most extremely ill patients	4 (6.8)	5 (8.5)	3 (5.1)	NR	NR
Missing	1 (1.7)	0	0	NR	NR

Abbreviations: BMI, body mass index; ESS, Epworth Sleepiness Scale; MWT20, 20 minute Maintenance of Wakefulness Test; MWT40, 40 minute Maintenance of Wakefulness Test; NA, not applicable; NR, not reported; qd, once daily; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
† Mean CGI-s score at baseline was 5 for each treatment arm, indicating markedly ill patients; no breakdown by CGI-s score was reported.
Source: Thorpy 2019 (28); CSR Table 7 (29).

A29. Please add data (where available) to the baseline characteristics reported in Tables 17 and 18 (D.1.5.1) on the proportions of patients in each of the baseline clinician global impression of severity (CGI-s) score categories (or an alternative severity scale if studies have used an alternative to the CGI-s).

Only TONES-2 and Xyrem, 2005 provided CGI-s values - no other studies provided CGI-s or a similar clinician-assessed measure. Black, 2006 reports “The baseline CGI-s assessment indicated that the patients enrolled in the study were considered to be markedly ill despite treatment with modafinil.” Numerical values of CGI-s are not reported in this or secondary publications from this trial. CGI-s data for TONES 2 and the Xyrem 2005 study, respectively are in Table 15 and Table 16 below (equivalent to Table 17 and 18 in the original CS).

Table 16. Baseline characteristics of included trials assessing pitolisant and sodium oxybate

	Dauvilliers, 2013			Szakacs, 2017		Xyrem, 2002				Xyrem, 2005				Black, 2006	
Treatment arm	**Placebo**	**Pitolisant 10-40 mg qd**	**Modafinil 100-400 mg qd**	**Placebo**	**Pitolisant 5-40 mg qd**	**Placebo**	**Sodium oxybate 3 g qd**	**Sodium oxybate 6 g qd**	**Sodium oxybate 9 g qd**	**Placebo**	**Sodium oxybate 4.5 g bd**	**Sodium oxybate 6 g bd**	**Sodium oxybate 9 g bd**	**Placebo**	**Sodium oxybate 6-9 g qd**
N	30	31	33	51	54	34	34	33	35	59	64	58	47	55	50
Cataplexy, %	80	81	82	100	100	100	100	100	100	100	100	100	100	58	28
Age, mean, y	NR	NR	NR	NR	NR	40.8	43.8			40.8	41.8	39.2	39.9	41	35.1
Age, median, y	39.5	33.0	40.0	39	34	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Age range, y	NR	NR	NR	53	48	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Males, %	43	65	55	53	48	35	44			29	33	38	40	44	52
Caucasian, %	90	94	97	28.8	27.2	85	93			92	78	85	92	78	94
BMI, mean, kg/m^2	28.2	30.4	27.7	17.4	17.3	NR	NR	NR	NR	29.1	30.0	32.1	30.1	NR	NR
ESS, mean	18.9	17.8	18.5	17.4	17.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ESS, median	NR	NR	NR	NR	NR	19.0	17.0	17.6	17.1	17.5	18.0	19.0	19.0	16.0	15.0
MWT20	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	9.7	11.3
MWT40	8.4	7.4	8.8	4.1	3.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baseline CGI-s, n (%)															
Normal	Not Reported for these studies									0	0	0	0	See above narrative for A29	
Borderline ill										1 (1.7)	0	2 (3.4)	0		
Mildly ill										3 (5.1)	5 (7.8)	4 (6.9)	5 (10.6)		
Moderately ill										25 (42.4)	24 (37.5)	24 (41.4)	12 (25.5)		
Markedly ill										25 (42.4)	28 *43.8)	25 (43.1)	24 (51.1)		
Severely ill										NR†	NR†	NR†	NR†		

	Dauvilliers, 2013			Szakacs, 2017		Xyrem, 2002				Xyrem, 2005				Black, 2006	
Treatment arm	**Placebo**	**Pitolisant 10-40 mg qd**	**Modafinil 100-400 mg qd**	**Placebo**	**Pitolisant 5-40 mg qd**	**Placebo**	**Sodium oxybate 3 g qd**	**Sodium oxybate 6 g qd**	**Sodium oxybate 9 g qd**	**Placebo**	**Sodium oxybate 4.5 g bd**	**Sodium oxybate 6 g bd**	**Sodium oxybate 9 g bd**	**Placebo**	**Sodium oxybate 6-9 g qd**
Among the most extremely ill patients										5 (8.5)	7 (10.9)	3 (5.2)	5 (10.6)		
Missing										0	0	0	1 (2.1)		

Abbreviations: bd, twice daily; 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.

† This category of the CGI-s was not reported in the Xyrem 2005 publication (30).

A30. Appendix D Table 18 reports on the percentage of patients with cataplexy. In the Black 2006 study this is lower than for the other studies and the proportion differs markedly between the placebo and sodium oxybate arms. The ERG have not been able to find the proportion of patients at baseline reported in the Black 2006 paper (25). Please would the company check these values, confirm whether they are correct and indicate where they have been obtained from.

Cataplexy incidence was obtained from Black, 2016 (Black, Jed, et al. Impact of sodium oxybate, modafinil, and combination treatment on excessive daytime sleepiness in patients who have narcolepsy with or without cataplexy. Sleep Med. 2016;24 (2016): 57-62 (31)), which is a secondary reference to Black, 2006 (25). Table 1 in Black, 2016 confirms the numbers found in CS Appendix D, Table 18 (see Table 17).

Table 17. Cataplexy Prevalence from Black, 2006 (Derived from Black, 2016)

	Placebo (n = 55)	Sodium oxybate 6-9 g once daily (n = 50)
Patients with cataplexy, N (%)	32 (58)	14 (28)
Patients without cataplexy, N (%)	23 (42)	36 (72)

A31. Priority question: Appendix D, D.1.5.6 presents a scenario analysis comparing 12-week outcomes for solriamfetol against the last available timepoint for comparator trials. To ensure our understanding of the data that contribute to this analysis, please provide a table showing which data were included (similar format to CS Appendix D Table 9).

ESS week 12

Table 18. Scenario Analysis, ESS Input

Trial	Timepoint, week	Treatment, qd	N	Mean	SE	Notes	Imputation Calculation
TONES 2	12	Placebo	52	-1.6	0.65	-	-
		Solriamfetol 75 mg	49	-3.8	0.67		
		Solriamfetol 150 mg	52	-5.4	0.66		
Dauvilliers, 2013	8	Placebo	25	-3.4	0.84	SE calculated from SD using N	-
		Pitolisant ≤40 mg	26	-5.8	1.22		
Szakacs, 2017	7	Placebo	51	-1.9	0.71	SE imputed as weighted average of available Placebo SEs	$\frac{[(0.65 * 52) + (0.84 * 25)]}{(52 + 25)}$
		Pitolisant ≤40 mg	54	-5.4	0.75	SE imputed as weighted average of all available SEs	$\frac{[(0.65 * 52) + (0.67 * 49) + (0.66 * 52) + (0.84 * 25) + (1.22 * 26)]}{(52 + 49 + 52 + 25 + 26)}$

Trial	Timepoint, week	Treatment, qd	N	Mean	SE	Notes	Imputation Calculation
Xyrem, 2005	8	Placebo	58	-0.5	0.71	SE imputed as weighted average of available Placebo SEs	$\frac{[(0.65 * 52) + (0.84 * 25)]}{(52 + 25)}$
		Sodium oxybate 4.5 g	61	-1	0.75	SE imputed as weighted average of all available SEs	$\frac{[(0.65 * 52) + (0.67 * 49) + (0.66 * 52) + (0.84 * 25) + (1.22 * 26)]}{(52 + 49 + 52 + 25 + 26)}$
		Sodium oxybate 6 g	55	-2	0.75		
		Sodium oxybate 9 g	43	-5	0.75		
Black, 2006	8	Placebo	53	0	0.71	SE imputed as weighted average of available Placebo SEs	$\frac{[(0.65 * 52) + (0.84 * 25)]}{(52 + 25)}$
		Sodium oxybate 9 g	49	-3	0.75	SE imputed as weighted average of all available SEs	$\frac{[(0.65 * 52) + (0.67 * 49) + (0.66 * 52) + (0.84 * 25) + (1.22 * 26)]}{(52 + 49 + 52 + 25 + 26)}$

Section B: Clarification on cost-effectiveness data

Patient population

B1. Please explain why the baseline characteristics of the model cohort are based on the 150mg mITT population of TONES 2. We suggest that the population characteristics should reflect those of the whole eligible population recruited to the trial, regardless of the allocated treatment (239 patients randomised).

The model utilises the IPD data for the 150 mg arm of TONES 2 to synthesise the pseudo-IPD data for the comparators considered. As a consequence, the baseline characteristics are limited to those of the 150 mg arm rather than the entire cohort. The starting age and gender will have minimal impact on the overall outcomes as these parameters will be consistent in all arms modelled. The analysis in response to question A25, utilising the 75 mg arm of TONES 2, demonstrates that whilst varying the baseline characteristics may result in small changes to QALYs gained and costs, the overall results remained consistent.

B2. We note that the EFNS guidelines for the management of narcolepsy recommend sodium oxybate “where EDS is concomitant to cataplexy and poor sleep” (CS B.1.3). Please conduct a cost-effectiveness scenario analysis using clinical effectiveness results for the subgroup with cataplexy. What effect does cataplexy have on utility and is there any evidence that cataplexy changes over time (we note that cataplexy is not included in the NHWS utility equation).

Solriamfetol is indicated to improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy) and not to address cataplexy itself. The NICE scope for the current assessment also focused on the impact of excessive sleepiness and cataplexy was not considered an outcome of interest.

Since there is no evidence to suggest solriamfetol would impact cataplexy, nor was it a requirement of the NICE scope, we have not assessed the impact of cataplexy within the cost-effectiveness analysis.

Analyses reported by Dodel 2007 (32) failed to detect an association between QoL and either improvement in cataplexy symptoms or in nocturnal sleep quality. The only impact on utility came from excessive daytime sleepiness and continuous sleep,

and daytime sleepiness is usually assessed using the ESS. A number of other studies (30, 33-35) also reported sleepiness as the main symptom of narcolepsy with cataplexy, and this is in keeping with expert opinion. We would therefore assume that there would be no impact on utility with the inclusion of cataplexy within the analysis.

In addition, we are unaware of any published evidence that supports that there is a change in cataplexy over time. Based on KOL Clinical Practice Interviews, there was limited clinical opinion that cataplexy may slightly improve in some patients, associated with aging over decades, however some clinicians also felt that there was no such effect and that this reflected adaptation to the condition over time.

B3. Please discuss what evidence there is, either from the literature or perhaps from investigations of the NHWS dataset, regarding how the symptoms and severity of narcolepsy change over time. For example, does ESS change with patient age or with time since diagnosis?

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.

Utilities

B4. Priority question: We anticipate that the NICE committee will want to see a scenario analysis with utilities estimated directly from EQ-5D-5L trial data, in addition to the results based on the NHWS and McDaid mappings. We understand the arguments regarding differences between the impacts of ESS in US and European populations. Nevertheless, these are speculative and applicability of the alternative datasets is open to question. We suggest that IPD data from the TONES 2 trial should be analysed with a regression approach to estimate mean utility by ESS score and/or direct differences in utility for responders/ non-responders. Covariate

adjustment could be applied to test for differences by treatment arm, US/EU patient and other potential confounders. Given the contention that the relationship between ESS and utility is stable across OSA and narcolepsy, this could be tested by analysis of the whole TONES 5 dataset (n=643) with covariate and interaction terms for condition.

As noted in the submission, a significant majority (~80–90%) of patients in the TONES 2 study reported either no problem or only a slight problem with their quality of life at baseline (as assessed using EQ-5D). Furthermore, these patients reported themselves as being less impaired, on average, compared with the general non-narcoleptic population in a number of subdomains of the EQ-5D, despite the fact that the majority of these patients were reported by investigators as being moderately (~25%), markedly (~40%) or severely ill (~25%) (assessed using the CGI-s).

Jazz Pharmaceuticals have so far been unable to reconcile the observed quality of life/EQ-5D baseline data from TONES 2, and the patients' quality of life responses with the widely accepted clinical and patient perspective from other data sets (such as British Lung Foundation, Narcolepsy UK, National Health and Wellness Survey and, McDaid), which demonstrate that the actual impairment in quality of life associated with EDS is substantial. Given this clear inconsistency between the TONES quality of life data (assessed using the generic EQ-5D) and the information on the real-world impact that EDS due to narcolepsy has on patients' lives, Jazz Pharmaceuticals still conclude that the use of the TONES data would be inappropriate for inclusion within this analysis.

The currently available evidence from the clinical trials and the associated ITC show that the efficacy of the main comparators is broadly comparable, but that solriamfetol has significantly lower cost than both pitolisant and sodium oxybate. As such, the impact of alternative utility estimates is unlikely to change the conclusions of the cost-effectiveness analysis (with solriamfetol dominating sodium oxybate or being cost-effective, in the South-West quadrant, compared with pitolisant). However, Jazz will continue to review this data set, bearing in mind the ERG advice.

Clinical effects

B5. Priority question: Could you please clarify the formulae used to estimate individual ESS changes from baseline for each treatment (company model Sheet _IPD_Narc)? For instance, in cell N7, =IF(AND($G7>10,$F7=L4),IF($G7-N$4>24,24-$G7,IF($G7-N$4<0,-$G7,$L7-N$4)),""): Please clarify what the number 10 stands for and why it is relevant in the above formula. Please clarify what the number 24 stands for and why it is relevant in the above formula.

The '>10' against the values in column G is a check on the baseline patient characteristics to ensure that only those patients with a baseline ESS greater than 10 are included. The ESS ranges from 0–24/1–24 and is therefore bound between 0 and 24. The intention of the remainder of the formula is to ensure that the projected ESS values cannot exceed these bounds.

Costs

B6. Please explain the company position that the protocol-driven titration of solriamfetol dose in TONES 5 does not provide a representative breakdown of how solriamfetol would be administered in practice (CS B.3.5.1)? The 300 mg dose would not be available, but the open label data is available to estimate the mix of maximum tolerated (and licensed) dose (E.g. [redacted] for 75 mg and ([redacted]) days for 150 mg, or similar, based on the 'modal dose' distribution). Please provide scenario analysis using this method.

The protocol-driven titration used in TONES 5 directed investigators to titrate patients to the highest tolerated dose at intervals of at least 3 days, in order to achieve rapid stabilisation on the maximally effective dose (300 mg, unlicensed). Titration was not based on objective measures of clinical benefit or response (such as change in ESS) specifically, but was instead based on whether or not the dose was tolerated. Titration therefore occurred relatively quickly in the study, due to the guidance to wait only for a minimum of 3 days before titrating.

Feedback from the KOL Clinical Practice Interviews informs that, as is common practice in the UK, clinicians will likely titrate solriamfetol slowly, and based on clinical effectiveness and tolerability. The clinical intention is to maintain patients on the lowest effective and tolerated dose, rather than titrating to the highest tolerated

dose. This will most likely result in a noticeably different dose distribution to that created by the use of the titration practices used in TONES 5, and therefore using the open label data to estimate the maximum tolerated dose would be inappropriate and would not reflect the expected usage of solriamfetol in UK clinical practice.

To date, clinical experience in the US is consistent with the anticipated UK approach, with ~50% of patients remaining on the lowest dose (75 mg) of solriamfetol.

Economic model

B7. Priority question: Please provide a rationale for applying the normal distribution to the mean change in ESS relative to solriamfetol 150 mg for comparators in the company's PSA. An IPD plot of ESS change from baseline for all comparators shows negative skewness. Please provide a revised PSA based on a more appropriate distribution for the mean change in ESS.

The solriamfetol 150 mg IPD has a negative skew and so this will implicitly result in a negative skew in the comparator data, generated with the pseudo-IPD. The mean change in ESS, relative to solriamfetol 150 mg, is based on the output of an ITC and there is no detail available to ascertain any skew that could be applied.

As such, it was assumed that the central limit theorem would apply and a normal distribution was assumed for the mean change in ESS for all comparators relative to solriamfetol 150mg.

B8. Please justify the appropriateness of the integration of bootstrapped IPD data in the PSA calculations. A basic principle of the non-parametric bootstrap approach is that the size of the re-sampled datasets should be the same as the original real-world data sample: to reflect the magnitude of sampling variation.(36) Thus each PSA iteration should combine results from one non-parametric bootstrap sample of the same size as the original TONES 2 150mg 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 base case analysis is based on 5,000 bootstrap samples and so it was assumed that drawing 5,000 bootstrap samples for each PSA iteration would allow for a consistent point of reference. However, we recognise the ERG's concern 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). Results are shown in in Appendix A.

B9. Priority question. We have identified errors in the formulas for calculating standard deviations and confidence intervals for bootstrap results and PSA results (see Rows 6 and 7 in model sheets bootstrap_Simulations and PSA Simulations. The range of rows picked up is incorrect, shifted up by 4 rows) Please correct these errors in the model.

Thank you for notifying us of this error. It appears the issue will impact the standard error estimates for the bootstrapped and PSA outputs and will have resulted in an underestimation of the associated confidence intervals. The revised confidence intervals are presented in Appendix A. (Base case results: Table 19, PSA results: Table 20 and Figure 8. Cost-effectiveness acceptability curve).

B10. Priority question. Univariate results presented for Solriamfetol versus pitolisant (Table 53 and Figure 22) do not match with model rerun of sensitivity analysis (see results in Univariate analysis sheet in company model). Please explain this discrepancy. In addition, discontinuation loss of effect for Sol 150mg and discontinuation due to TEAEs (year 1) for Sol 150mg were excluded from CS Table 53. These two parameters are among the 10 with the greatest impact on cost-effectiveness. Please provide justification for excluding these parameters or update results to include them. Similarly, please update results for threshold analysis for solriamfetol versus pitolisant with these parameters or provide justification for excluding them.

It appears that a small error was introduced into the model after the univariate analysis was generated that led to the discrepancy identified by the ERG. Specifically, cells G36, G42 and G44 of the _Parameters tab included a formula rather than the default figure of 10.9%. Similarly, G60 contained a formula rather than the default value of 4.4%. Addressing these issues aligns the model univariate sensitivity analysis rerun with the results already presented in CS Table 53 and Figure 22 and also means CS Table 53 is correct.

The two excluded parameters are those the ERG have identified in the model rerun, which included the error detailed above. These parameters are not in the top 10 in

the revised model. Please note that the model does consider these and all other model parameters in the univariate analysis.

B11. Please note that model results for PSA and the content of CS table 52 do not match. Please clarify if this is because the company has reported a different run of PSA for 10,000 iterations. Similarly, CS Figure 20 does not match model plot, even though both plots bear close resemblance.

The CS Table 52 and model are different runs of PSA. The PSA has been re-run to account for B8 and the revised results are presented in the Appendices. CS Figure 20 represents the results of the bootstrapped base case (CS Table 28) presented on the cost-effectiveness frontier and not the results of the PSA. The results of the PSA have not been presented on the cost-effectiveness frontier but rather on the cost-effectiveness acceptability curve (CS Figure 21).

B12. Priority question. The ERG is unable to replicate the scenario analyses (Tables 58-86). There appears to be an error in company model VBA codes which prevents code from running. A 'ScenarioAnalysis' sheet is mentioned in the VBA code but is missing from the company's model. Please clarify or correct as appropriate.

The majority of the scenario results have been generated manually from within the model, adjusting key parameters as required.

The ScenarioAnalysis macro was a remnant of a model template and has not been utilised to generate any of the scenario results (due to the multiple output requirements for the various scenarios).

Apologies for any confusions this may have caused.

B13. Mean ESS in responders and non-responders (CS Table 41) is reported in CS but doesn't seem to be used directly for estimating cost-effectiveness in model. Please clarify this discrepancy.

The mean ESS scores for responders and non-responders were utilised in the NHWS mapping algorithm to estimate utilities. The corresponding utilities are presented in CS Table 43 although it should be noted that the actual utilities will vary over time due to the age component with the NHWS mapping algorithm.

Section C: Textual clarification and additional points

C1. Appendix D, Section D.1.5.1 'Patient Characteristics' states "Patient demographics were found to be generally similar across studies (characteristics of solriamfetol and modafinil trials, Table 17;". The ERG notes Table 17 contains baseline characteristics of solriamfetol trials only and that the company have not included modafinil in the NMA. We presume this is a typographical error, please confirm if this is the case.

Correct. The sentence should say "Patient demographics were found to be generally similar across studies (characteristics of solriamfetol trials, Table 17; characteristics of pitolisant and sodium oxybate trials, Table 18)."

Section D: Additional requests from NICE project team

D1. Please provide the European public assessment report (EPAR) for solriamfetol. Please ensure that no information published in the EPAR is marked as AIC in the company submissions and update the confidentiality marking if necessary.

This has been provided as a separate document "ID1602 Solriamfetol ERG clarification_EPAR".

D2. Please provide redacted versions of all submissions that have confidential information and for submissions that include both academic and commercial in confidence information, please provide a version with academic in confidence marking and commercial in confidence information redacted.

Redacted versions will be provided prior to the publication of the submission documents on the NICE website.

References

1. Broderick JE, Junghaenel DU, Schneider S, Pilosi JJ, Stone AA. Pittsburgh and Epworth sleep scale items: accuracy of ratings across different reporting periods. Behav Sleep Med. 2013;11(3):173-88.
2. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65.
3. Wahlqvist P, Carlsson J, Stalhammar NO, Wiklund I. Validity of a Work Productivity and Activity Impairment questionnaire for patients with symptoms

of gastro-esophageal reflux disease (WPAI-GERD)--results from a cross-sectional study. Value Health. 2002;5(2):106-13.
4. Reilly MC, Lavin PT, Kahler KH, Pariser DM. Validation of the Dermatology Life Quality Index and the Work Productivity and Activity Impairment-Chronic Hand Dermatitis questionnaire in chronic hand dermatitis. J Am Acad Dermatol. 2003;48(1):128-30.
5. Wahlqvist P, Guyatt G, Armstrong D, Austin P, Barkun A, Chiba N, et al. Pgi9 Responsiveness to Change and English Language Validation of the Wpai-Gerd Questionnaire-Results from a Canadian Study. Value in Health. 2004;7(3).
6. Kobelt G, Borgstrom F, Mattiasson A. Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. BJU Int. 2003;91(3):190-5.
7. Andreasson E, Svensson K, Berggren F. Prp11 the Validity of the Work Productivity and Activity Impairment Questionnaire for Patients with Asthma (Wpaiasthma): Results from a Web-Based Study. Value in Health. 2003;6(6).
8. Reilly MC, Bracco A, Ricci JF, Santoro J, Stevens T. The validity and accuracy of the Work Productivity and Activity Impairment questionnaire--irritable bowel syndrome version (WPAI:IBS). Aliment Pharmacol Ther. 2004;20(4):459-67.
9. Perrillo R, Rothstein KD, Rubin R, Alam I, Imperial J, Harb G, et al. Comparison of quality of life, work productivity and medical resource utilization of peginterferon alpha 2a vs the combination of interferon alpha 2b plus ribavirin as initial treatment in patients with chronic hepatitis C. J Viral Hepat. 2004;11(2):157-65.
10. Tanner LA, Reilly MC, Meltzer EOB, J. E., , J. M. Effect of Fexofenadine HC1 on Quality of Life and Work, Classroom, and Daily Activity Impairment in Patients with Seasonal Allergic Rhinitis. American Journal of Managed Care. 1999;5(4 (Supp)):S235-S47.
11. Meltzer EO, Casale TB, Nathan RA, Thompson AK. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. Annals of Allergy, Asthma & Immunology. 1999;83(4):311-7.
12. Jacobs RJ, Davidson JR, Gupta S, Meyerhoff AS. The effects of clonazepam on quality of life and work productivity in panic disorder. Am J Manag Care. 1997;3(8):1187-96.
13. Botokeky E, Freymond N, Gormand F, Le Cam P, Chatte G, Kuntz J, et al. Benefit of continuous positive airway pressure on work quality in patients with severe obstructive sleep apnea. Sleep Breath. 2019;23(3):753-9.
14. Dean B, Aguilar D, Shapiro C, Orr WC, Isserman JA, Calimlim B, et al. Impaired health status, daily functioning, and work productivity in adults with excessive sleepiness. Journal of occupational and environmental medicine. 2010;52(2):144-9.
15. DiBonaventura M, Richard L, Kumar M, Forsythe A, Flores NM, Moline M. The Association between Insomnia and Insomnia Treatment Side Effects on Health Status, Work Productivity, and Healthcare Resource Use. PLoS One. 2015;10(10):e0137117.
16. Fitzgerald T, Vietri J. Residual Effects of Sleep Medications Are Commonly Reported and Associated with Impaired Patient-Reported Outcomes among Insomnia Patients in the United States. Sleep Disord. 2015;2015:607148.

17. Kimball AB, Edson-Heredia E, Zhu B, Guo J, Maeda-Chubachi T, Shen W, et al. Understanding the Relationship Between Pruritus Severity and Work Productivity in Patients With Moderate-to-Severe Psoriasis: Sleep Problems Are a Mediating Factor. Journal of Drugs in Dermatology : JDD. 2016;15(2):183-8.
18. Jazz Pharmaceuticals. **CONFIDENTIAL**. TONES 5 Clinical study report. A long-term safety and maintenance of efficacy study of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy or obstructive sleep apnoea. 2018.
19. Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: systematic review and meta-analysis. Medical science monitor : international medical journal of experimental and clinical research. 2010;16(8):Ra177-86.
20. Lehert P, Falissard B. Multiple treatment comparison in narcolepsy: a network meta-analysis. Sleep. 2018;41(12).
21. Balk E, Earley A, Patel K, Trikalinos T, Dahabreh I. Empirical assessment of within-arm correlation imputation in trials of continuous outcomes. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK115797/. Accessed on: 28th August 2020
22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(1):13.
23. The Cochrane Collaboration. Imputing standard deviations for changes from baseline. 2011. Available from: https://handbook-5-1.cochrane.org/chapter_16/16_1_3_2_imputing_standard_deviations_for_changes_from_baseline.htm. Accessed on: 28th August 2020
24. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol. 2013;12(11):1068-75.
25. Black J, Houghton W. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep. 2006;29(7):939-46.
26. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998;43(1):88-97.
27. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology. 2000;54(5):1166-75.
28. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3):359-70.
29. Jazz Pharmaceuticals. **CONFIDENTIAL.** TONES 2 Clinical study report. A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy. . 2017.
30. Xyrem® International Study Group (A). A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med. 2005;1(4):391-7.
31. Black J, Swick T, Bogan R, Lai C, Carter LP. Impact of sodium oxybate, modafinil, and combination treatment on excessive daytime sleepiness in

patients who have narcolepsy with or without cataplexy. Sleep Med. 2016;24:57-62.
32. Dodel R, Peter H, Spottke A, Noelker C, Althaus A, Siebert U, et al. Health-related quality of life in patients with narcolepsy. Sleep Medicine. 2007;8(7-8):733-41.
33. US Xyrem® Multicenter Study Group. The abrupt cessation of therapeutically administered sodium oxybate (GHB) does not cause withdrawal symptoms. Journal of toxicology Clinical toxicology. 2003;41(2):131-5.
34. US Xyrem® Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep. 2002;25(1):42-9.
35. Xyrem® International Study Group (B). Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. Sleep Med. 2005;6(5):415-21.
36. Efron B, Tibshirani R. An Introduction to the Bootstrap: Chapman and Hall, New York, London; 1993.

Appendix A.

Revised results to address questions B8 and B9 are provided below.

Table 19. Base-case results – By dose

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER versus baseline (£/QALY)	ICER versus solriamfetol 150mg (£/QALY)
Solriamfetol 75mg	£5,975 (£5,970 - £5,981)	13.273 (13.268 - 13.277)	42.044 (42.014 - 42.073)					£70,702*
Solriamfetol 150mg	£10,766 (£10,759 - £10,773)	13.341 (13.336 - 13.345)	42.044 (42.014 - 42.073)	£4,791	0.068	£70,702	£70,702	
Sodium Oxybate 4.5g	£11,473 (£11,459 - £11,486)	13.203 (13.199 - 13.208)	42.044 (42.014 - 42.073)	£707	-0.137	Dominated	Dominated	Dominated
Pitolisant ≤ 40mg	£20,991 (£20,977 - £21,004)	13.341 (13.336 - 13.346)	42.044 (42.014 - 42.073)	£9,518	0.138	£69,120	Extendedly dominated	Extendedly dominated
Sodium Oxybate 6g	£22,587 (£22,568 - £22,606)	13.272 (13.267 - 13.276)	42.044 (42.014 - 42.073)	£1,596	-0.069	Dominated	Dominated	Dominated
Sodium Oxybate 9g	£43,532 (£43,504 - £43,559)	13.346 (13.342 - 13.351)	42.044 (42.014 - 42.073)	£20,945	0.075	£280,171	£509,641	£5,521,622*

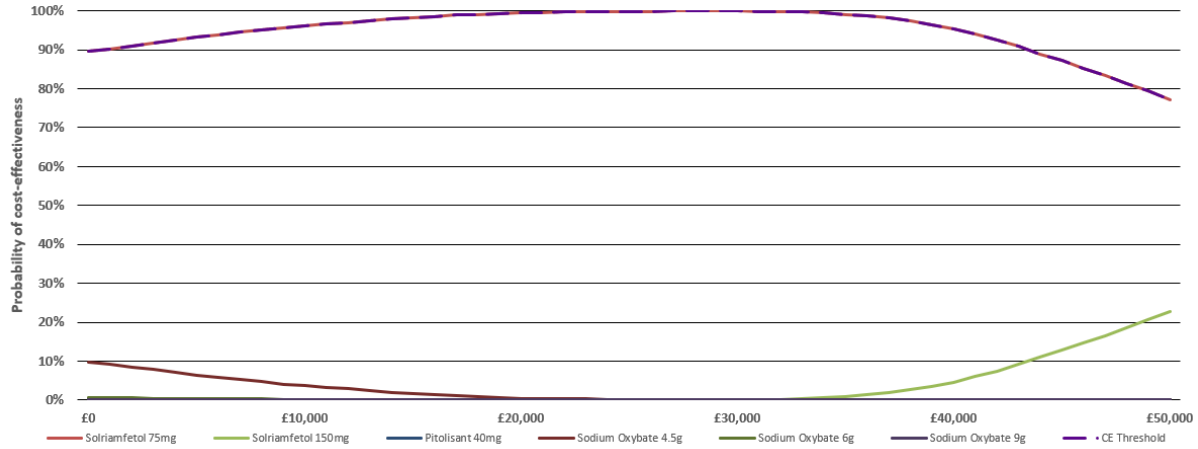
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. * South-West Quadrant of cost-effectiveness plane

Table 20. Probabilistic sensitivity analysis results

Technologies	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Solriamfetol 75mg	£5,303 (£5,272 - £5,334)	13.227 (13.211 - 13.243)				
Solriamfetol 150mg	£10,774 (£10,749 - £10,799)	13.317 (13.301 - 13.334)	£5,471	0.090	£60,534	£60,534
Sodium Oxybate 4.5g	£10,976 (£10,881 - £11,071)	13.173 (13.157 - 13.190)	£202	-0.144	Dominated	Dominated
Sodium Oxybate 6g	£19,187 (£19,048 - £19,325)	13.219 (13.202 - 13.235)	£8,210	0.046	£180,357	Dominated
Pitolisant ≤ 40mg	£20,199 (£20,098 - £20,300)	13.309 (13.293 - 13.325)	£1,013	0.090	£11,212	Extendedly dominated
Sodium Oxybate 9g	£45,246 (£45,083 - £45,408)	13.333 (13.317 - 13.350)	£25,046	0.024	£1,031,962	£375,990

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Figure 8. Cost-effectiveness acceptability curve



At a threshold of £20,000 per QALY, the probability that solriamfetol 75 mg or 150 mg was the most cost-effective treatment was 99.49% or 0.00%, respectively (Figure 8). This resulted in a combined probability of 99.49% that solriamfetol would be cost effective at a willingness to pay threshold of £20,000 per QALY. At a threshold of £30,000 per QALY, this probability increases to 99.92% and 0.05% for the 75 mg and 150 mg formulations respectively. This resulted in a combined probability of 99.97% that solriamfetol would be cost-effective at a willingness to pay threshold of £30,000 per QALY. Across 10,000 PSA simulations, solriamfetol 75 mg was associated with a mean cost of £5,302 (95% CI: £5,271, £5,333) and a mean total QALYs of 13.227 (95% CI: 13.211, 13.243) while solriamfetol 150 mg was associated with a mean cost of £10,774 (95% CI: £10,749, 10,799) and mean a total QALYs of 13.317 (95% CI: 13.301, 13.334) (Table 20). These results are highly congruent with the deterministic results. The PSA results in a slight shift in the position of pitolisant in the full incremental analysis, dropping it between sodium oxybate 6 g and 9 g, but pitolisant remains extendedly dominated versus solriamfetol 75 mg. Overall the results remain consistent with the base case analysis with the solriamfetol doses demonstrating dominance or high cost-effectiveness over all other treatments considered in the analysis.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**
3. Job title or position	**Consultant neurologist**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	ABN is an organisation for all neurologists, including trainees in the UK, that aims to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. It is a not for profit organisation and mainly funded via membership fees.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**No**

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Treatment is symptomatic rather than curative and directed at the two main symptoms of the condition: - Excessive daytime sleepiness and - Cataplexy (loss of muscle tone usually associated with REM sleep but present in wakefulness) Treatment aims to reduce the impact and severity of the symptoms to reduce impact of the disorder by reducing sleepiness and risk of falling asleep in inappropriate situations, reduce or stop cataplexy attacks and associated risks of for example falls with these to improve quality of life and ability to carry out day to day activities both in work and social situations.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of scores on the Epworth Sleepiness Scale (ESS - a scale used to assess sleepiness ranging from 0-24 points with higher scores indicating worse symptoms) of 3 points is usually seen as a clinically relevant improvement. Reduction of cataplexy attacks >50% is often seen as significant. As the ESS is sometimes not seen as the most reliable tool to assess sleepiness, some studies have used Clinical Global Impression of Change instead and this is usually how we assess patients in clinical practice as this takes all factors (sleepiness, frequency as well as severity of cataplexy, mood, ability to live a more “normal life”) into account.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are limited treatment options for patients with narcolepsy (with and without cataplexy) and many of the current treatment options are associated with significant side effects or may be contraindicated in patients with other medical conditions, particularly cardiac co-morbidities. I understand the treatment may also be considered for patients with continued sleepiness despite adequately treated sleep apnoea. For this group of patients, there is currently no licenced treatment.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients are currently treated with a combination of stimulants (Modafinil, amphetamine derivatives and recently Pitolisant) for their excessive daytime somnolence and antidepressants for cataplexy. In patients with severe symptoms, who are not responding to this treatment, sodium oxybate is used. The availability of sodium oxybate varies across the country and in many instances IFRs are needed for adults even if this funded via NHS England for children.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are currently no national guidelines for the treatment of narcolepsy in the UK. There are guidelines from the European Federation of Neurological Societies (now called the European academy of neurology – EAN) that are currently being updated. Expected in 2020.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is no clearly defined pathway but the majority of clinicians in England tend to follow a similar path. Treatment of excessive daytime somnolence 1st line treatment – Modafinil 2nd line treatment – amphetamine derived stimulants (Dexamphetamine or Methylphenidate) 3rd line treatment – Sodium Oxybate or Pitolisant Currently 3rd line treatment options are not available across England and there is clear discrepancy in treatment options accessible for adults with narcolepsy, particularly as IFRs are regularly rejected for Sodium Oxybate applications. Outside England, Sodium Oxybate and Pitolisant are more readily available

	in other European countries and US. This is likely to be reflected in the European guidelines on narcolepsy treatment due next year. Cataplexy is treated with different antidepressants with Sodium Oxybate treatment in patients not responding to antidepressants.
• What impact would the technology have on the current pathway of care?	Solriamfetol would most likely be used as 3rd of 4th line treatment option depending on patient characteristics and co-morbidities. It would be a welcome addition to the limited treatment choices for this condition, particularly since many of the available treatment options have side effects and contraindications especially in patients with co-morbidities.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The treatment will be used in similar way to current treatments and patients followed in similar way in clinic.
• How does healthcare resource use differ between the technology and current care?	I am not familiar with the cost of the new treatment and am therefore not certain if the new drug would result in greater pharmacological cost. Patients will be followed in clinic in similar way to current treatments so is unlikely to change resources needed from a clinical management point of view.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment would be initiated in secondary care or specialist clinics with primary care taking over prescription once the patient was stable.
• What investment is needed to introduce the	No particular investments needed.

technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, particularly for patients who do not derive benefit from current treatments, have side effects or contraindications to current treatment options, I do expect the new treatment to have meaningful benefits.
• Do you expect the technology to increase length of life more than current care?	N/A
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially, particularly for patients who do not derive benefit from current treatments, have side effects or contraindications to current treatment options.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not clear to me.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Similar to current treatments, care and monitoring.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Similar to current practice with no additional tests required. Treatment will be started in patients with excessive daytime somnolence who has not responded to 1st and 2nd (and possibly 3rd) line treatment and stopped if it is deemed ineffective by patient and clinician or causing side effects.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Don't think so.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Slightly different mode of action to current options and may therefore be an important addition to treatment options for this patient group with limited options available.
• Is the technology a 'step-change' in the management of the condition?	Probably not but an important addition to treatment options.

• Does the use of the technology address any particular unmet need of the patient population?	Important addition to treatment options for narcolepsy where there are limited options available. For OSA patients with ongoing sleepiness despite CPAP, this will be a possibility to treat where there is currently no treatment licenced.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effect profile appears similar to current medication and I do not think this will affect management or QoL.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Probably.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Daytime somnolence, risk of falling asleep in the day in inappropriate situations, overall improvement of daytime function. These were measured in the trials.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. How do data on real-world experience compare with the trial data?	Not clear as the treatment has not yet been tried in any large patient populations outside the trials, at least none that have been reported and is available to me now.
Equality	
21a. Are there any potential equality issues that should be	There is currently significant variability in availability of treatment options for adults with narcolepsy across England where some trusts have easy access to treatment options only available to others via IFRs. The requirements for “exceptionality” stated in an IFR request exclude the majority of eligible patients for some

taken into account when considering this treatment?	potentially effective drugs (Zeman et al, BMJ 2016;353:i2367). It would therefore be vital that the same options are available to all eligible patients in England to reduce any inequality, not only for Solriamfetol but other currently available options as well.
21b. Consider whether these issues are different from issues with current care and why.	See point above.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Solriamfetol appears to be effective in treating daytime somnolence in patients with narcolepsy and OSA
- Although side effects and contraindications appear similar to current stimulants, there are limited treatment options for the conditions and additional treatment options are needed.
- There is currently significant variability in availability of treatment options for patients with narcolepsy across England and it would be important that the same options are available to all eligible patients in England to reduce any inequality, not only for Solriamfetol but other currently available options as well
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Martin B Allen**
2. Name of organisation	**University Hospital of North Midlands**

3. Job title or position	**Consultant Physician**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x** yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. Reduction in the excessive and intrusive sleepiness that debilitates patients with narcolepsy. 2. Improved quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. Practically a self-reported improvement during clinical interview. 2. Self-reported questionnaires do exist, e.g. the Epworth but are of limited value. 3. Objective measures such as a multiple wakefulness test are too time-consuming to be of clinical value.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes 1. Patients: diagnosis delayed / wrong diagnosis as patients do not present with a clearly identifiable history. 2. Healthcare professional's: failure to recognise. Patients may present with sleepiness and be thought to have sleep apnoea. A negative limited sleep study excludes sleep apnoea and patients may be discharged. There is often a failure to recognise the condition with one senior consultant quoting to me that "the condition of narcolepsy did not exist".
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	A secure diagnosis is made through a clinical history and objective measurements of a multiple sleep latency test preceded by overnight polysomnography. Alternative measures of looking at CSF Orexin are also available, though the latter does not document the objective nature of the sleepiness. There are a variety of guidelines that exist for management and treatment.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	EFNS guidelines on management of narcolepsy. European Journal of Neurology 2006, 13: 1035–1048
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The diagnostic pathway is clear but patients are not always recognised as having the symptoms associated with narcolepsy by all clinicians and therefore there may be a delay on onward referral to the appropriate secondary / tertiary centre for the appropriate sleep investigations. I.e. there is an issue of knowledge amongst patients, primary care physicians (who may only have one narcolepsy patient on their books) and both secondary care and general physician dealing with sleep problems about the subtlety of symptoms in patients with narcolepsy.
• What impact would the technology have on the current pathway of care?	Improved options of treatment.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The current management of narcolepsy is pharmacological and this new agent will be an additional sort of drug for managing narcolepsy, especially when patients are either intolerant or find the current medication ineffective.

• How does healthcare resource use differ between the technology and current care?	Diagnostic process will remain the same, the new medication will be an additional form of therapy that gives us additional treatment opportunities.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment should be initiated in specialist sleep centres in secondary or tertiary care in clinics where they have the appropriate experience to manage narcolepsy and have the associated diagnostic tools i.e. full polysomnography to assess patients.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional resources are required as the appropriate facilities exist in specialist sleep centres across the county.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The treatment is likely to be better tolerated than some of the standard therapies that have potentially cardio toxic side effects and are often impractical in administration. I believe therapy will be better tolerated, improving adherence and therefore outcomes for patients.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients should be under the regular review of a specialist sleep centre where the treatment can be both initiated, observed for effect and then stopped if necessary.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, I would expect an improved quality of life although current tools that we use for assessing improvements such as EQ5-D are insensitive. Simple sleep questionnaires such as the Epworth may show a reduction in sleepiness though have considerable variability. Specific sleep questionnaires do exist although they would be cumbersome to use in routine clinical practice.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	The “technology “ is not innovative but is an additional therapy in the current management of narcolepsy.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The current evidence shows an improvement in some patients who cannot tolerate current treatment and in that group it will certainly be a step wise improvement but generally the answer would be no.
• Does the use of the technology address any particular unmet need of the patient population?	There are a small number of patients that are intolerant of the current therapies and therefore an additional treatment option will be a useful intervention.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	While side effects may exist for many of the stimulants used in managing narcolepsy, the side effect profile of the current proposed drug seems to be better than many that exist.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	I do not believe any clinical trials have used wholly UK populations of patients however the standard diagnosis of narcolepsy across Europe is similar to that in the UK (apart from less provision of sleep laboratories) and therefore clinical trials from Europe are applicable to the UK.
• If not, how could the results be extrapolated to the UK setting?	As above.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in daytime sleepiness; improved quality of life; attainment / maintenance of driving licence; occupational history – return to gainful employment. Other outcomes such as the maintenance of wakefulness test have been used in clinical trials but are not applicable to routine clinical practice.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcomes are clinical evaluation together with perhaps some questionnaires. Long term outcomes are best observed through clinical history.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There may be anecdotal reports of the benefit of this drug but these should not form part of the formal evaluation and therefore a systematic review of trial evidence should be adequate to assess the benefit and proposed use within the narcolepsy population.
21. How do data on real-world experience compare with the trial data?	From anecdotal stories the effects described in trials are similar to those observed in “real life”.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are no issues particularly with equality. There are no race issues and whist individuals from lower social economic backgrounds may have a delay in undertaking formal assessment for their sleep problem this is not a true “inequality”.
22b. Consider whether these issues are different from issues with current care and why.	These issues are as above.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Additional medication for narcolepsy required as current therapies inadequate for some individuals.
- Raise the profile of narcolepsy
- Ensure that treatment is initiated and followed up in specialist sleep centres that have access to full polysomnography.
- Assessment should be predominantly clinical and subjective. .
- There are no inequalities

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

CONFIDENTIAL UNTIL PUBLISHED

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

Solriamfetol for treating excessive sleepiness caused by narcolepsy

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Irina Tikhonova, Senior Research Fellow (Health Technology Assessment and Modelling), SHTAC
Olu Onyimadu, Senior Research Assistant (Health Economics), SHTAC
David A. Scott, Director, Diligent Agile Synthesis Limited
Lorna Hazell, Senior Research Assistant, SHTAC
Jonathan Shepherd, Principal Research Fellow, SHTAC
Joanne Lord, Professorial Fellow, SHTAC
Joanna Picot, Senior Research Fellow, SHTAC

Correspondence to Joanna Picot, Senior Research Fellow, SHTAC
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute
Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

Date completed 13/03/2020

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 130155

Declared competing interests of the authors

None for the authors. Dr Tim Quinnell has been on the executive committee of the British Sleep Society since 2013 (including Treasurer 2015-2017 and then President until November 2019). The BSS receives sponsorship from companies for running its biennial scientific meeting (including from Jazz, Bioproject and UCB) but liaison with sponsors is conducted by a third party administrative company (also the event organiser). Dr. Andrew Hall attended a narcolepsy study day in May 2019 that was sponsored by Bioprojet/Lincoln Medical.

Acknowledgements

We are very grateful to Dr Tim Quinnell, Consultant Respiratory and Sleep Disorders Physician, Royal Papworth Hospital NHS Foundation Trust and Dr Andrew Hall, Consultant and Lead Clinician for Sleep Disorders Service, University Hospitals of Leicester NHS Trust who offered clinical advice and comments on the draft report. We would also like to thank: Lois Woods, Senior Research Assistant, SHTAC, for appraising the literature search strategies in the company's submission and Dr. Geoff Frampton, Senior Research Fellow, SHTAC, for providing a quality assurance review of the draft ERG report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Tikhonova, I.; Onyimadu, O.; Scott, D.A.; Hazell, L.; Shepherd, J; Lord, J.; Picot, J. Solriamfetol for treating excessive sleepiness caused by narcolepsy: A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2020.

Contributions of authors

Irina Tikhonova, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report. Olu Onyimadu, critically appraised the health economic systematic review, critically appraised the economic

evaluation, and drafted the report. David A. Scott, critically apprised the network meta-analyses, ran the ERG network meta-analyses and drafted the report. Lorna Hazell, critically appraised the clinical effectiveness systematic review and drafted the report. Jonathan Shepherd, critically appraised the clinical effectiveness systematic review and drafted the report. Joanne Lord, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report. Joanna Picot, critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor.

Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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][1] [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]

[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.

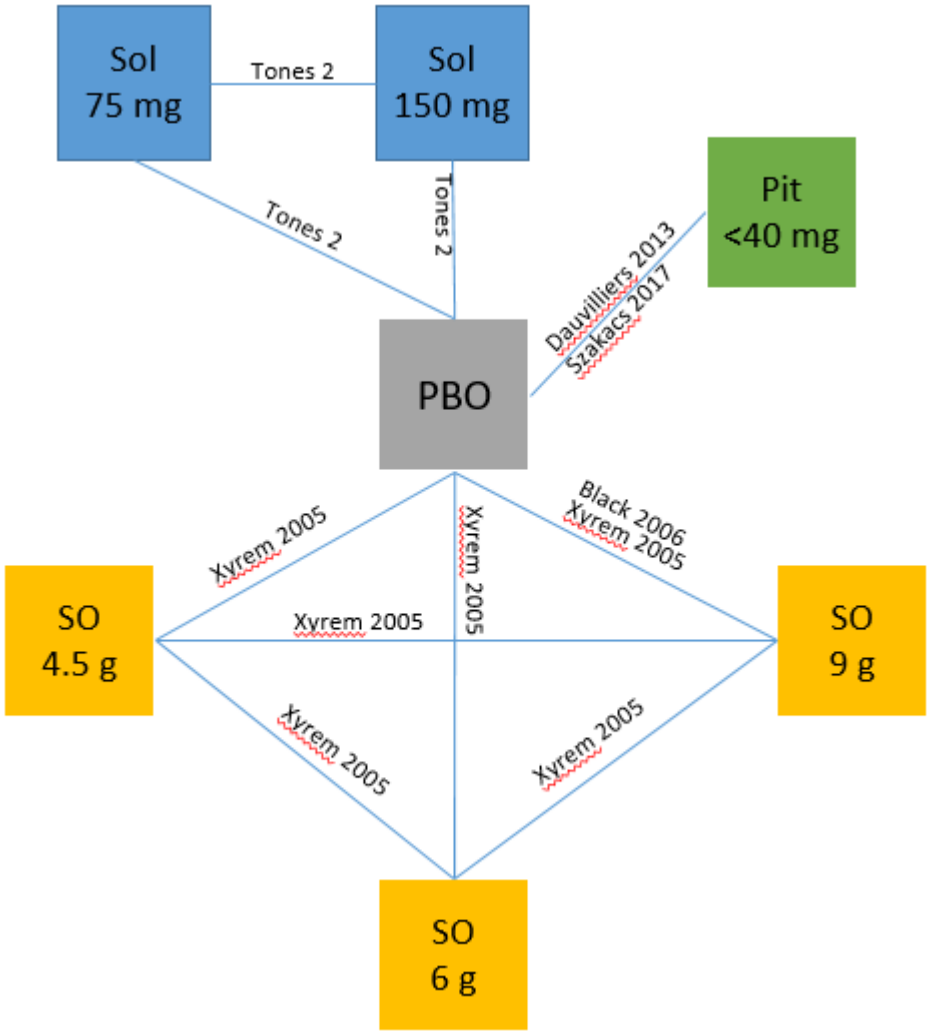


Figure 1 ESS 8-week NMA network diagram

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.

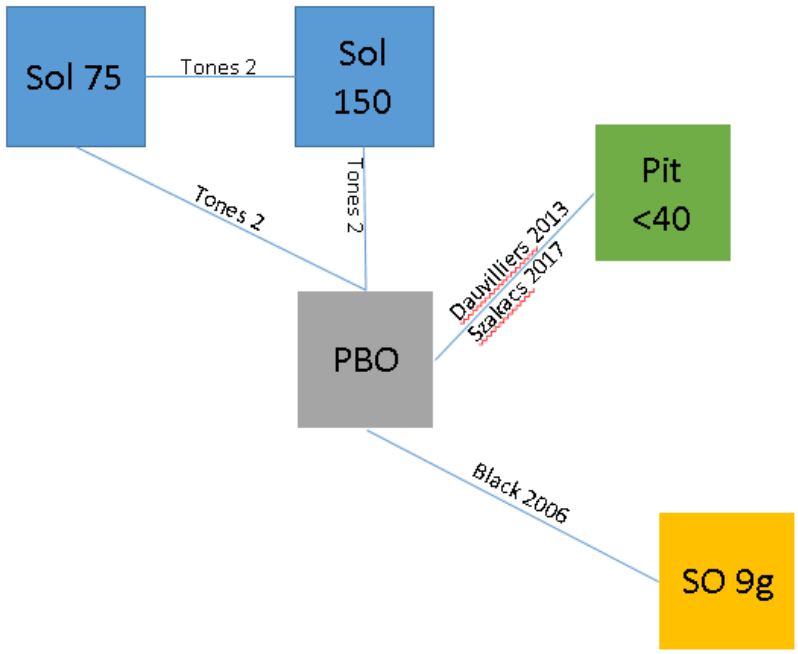


Figure 2 ESS 8-week NMA scenario: impact of concomitant therapy on sodium oxybate network diagram

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).

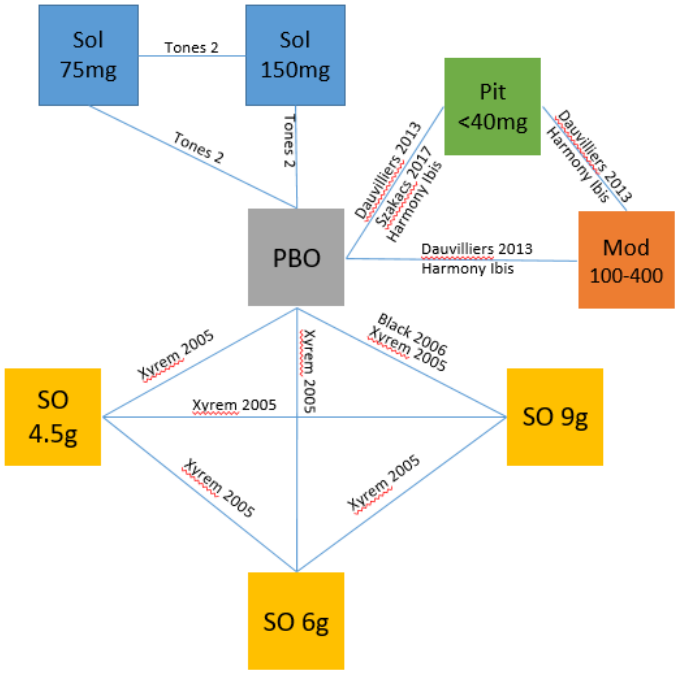


Figure 3 ERG's ESS week-8 network including modafinil and the Harmony Ibis trial

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

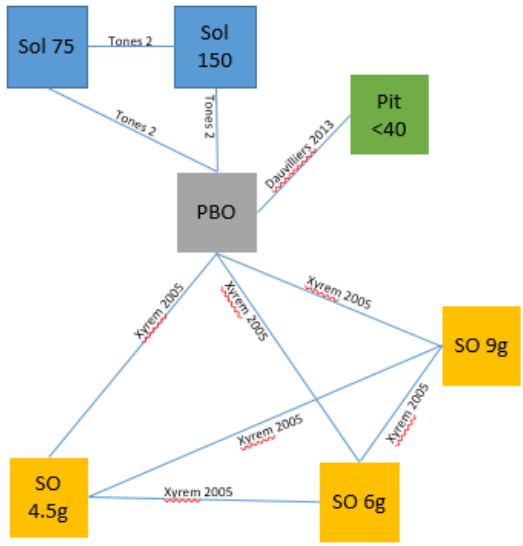


Figure 4 ERG's Serious TEAE network

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).

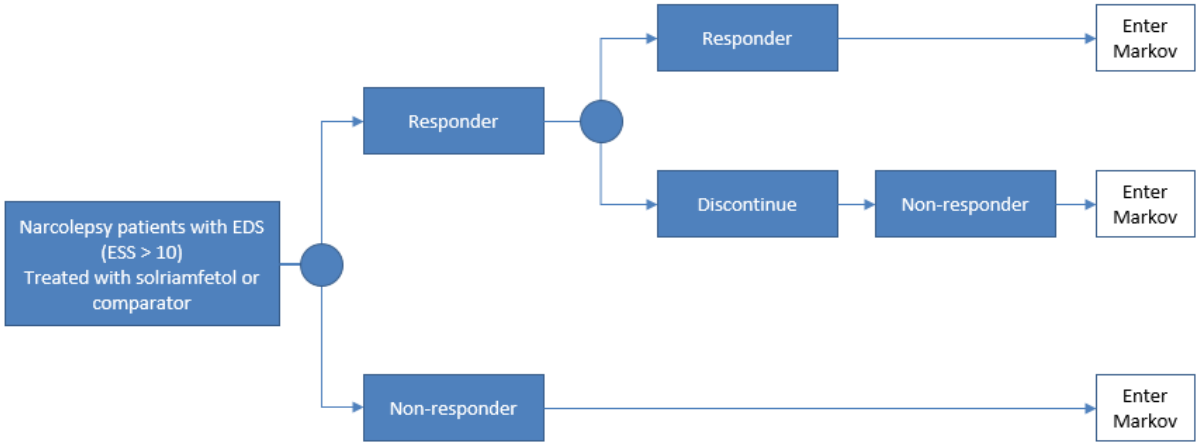


Figure 5 Treatment initiation – Decision tree

Source: reproduced from CS Figure 14

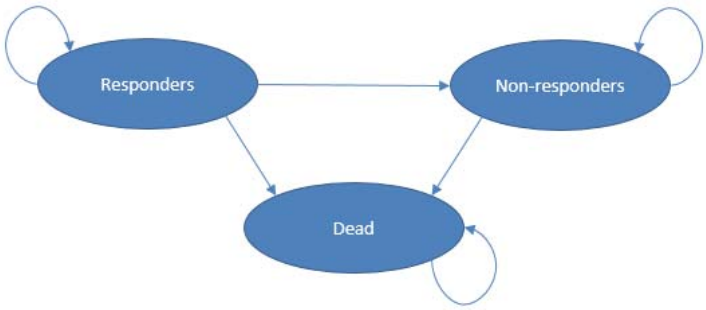


Figure 6 Maintenance treatment – Markov model

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.

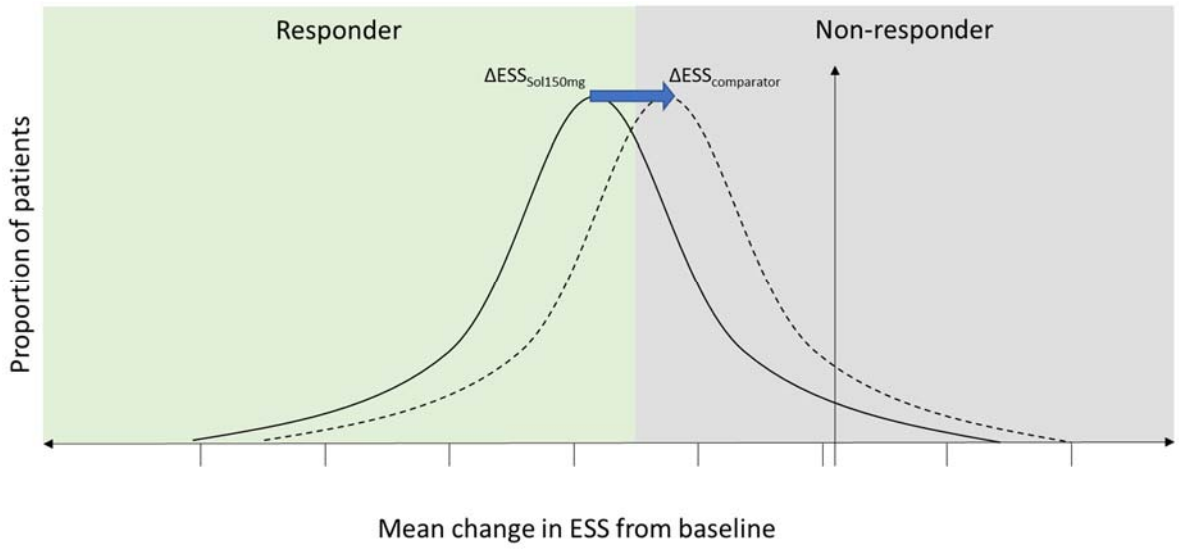


Figure 7 Transformation of IPD for comparator

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 [redacted]

Source: Extracted from CSR Table 14.2.6.2 by ERG

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

Source: Extracted from CSR Tables 14.2.10.2 by ERG

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

Source: Extracted from CSR Table 14.2.7.2 by ERG

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

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]

<u>Pilotisant</u>

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.

8 REFERENCES

1. Narcolepsy UK. About Narcolepsy 2019 [Available from: https://www.narcolepsy.org.uk/about-narcolepsy accessed 7 January 2020.
2. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 2014;146(5):1387-94. doi: 10.1378/chest.14-0970 [published Online First: 2014/11/05]
3. EMC. Summary of Product Characterisitics: Solriamfetol 2020 [Available from: https://www.medicines.org.uk/emc/product/11016/smpc accessed 13/03/2020.
4. National Institute for Health and Care Excellence. TA139 Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome 2008 [Available from: https://www.nice.org.uk/guidance/ta139/resources/continuous-positive-airway-pressure-for-the-treatment-of-obstructive-sleep-apnoeahypopnoea-syndrome-pdf-82598202209221 accessed 7 January 2020.
5. Institute of Health Economics (Alberta C. Quality Appraisal of Case Series Studies Checklist 2014 [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about accessed 7 January 2020.
6. Parkes J, Chen S, Clift S, et al. The clinical diagnosis of the narcoleptic syndrome. *Journal of Sleep Research* 1998;7(1):41-52. doi: 10.1046/j.1365-2869.1998.00093.x
7. Morrish E, King MA, Smith IE, et al. Factors associated with a delay in the diagnosis of narcolepsy. *Sleep medicine* 2004;5(1):37-41. doi: 10.1016/j.sleep.2003.06.002
8. Conolly A, Craig S. Overweight and obesity in adults and children: NHS Digital, 2019.
9. Dahmen N, Bierbrauer J, Kasten M. Increased prevalence of obesity in narcoleptic patients and relatives. *European Archives of Psychiatry and Clinical Neuroscience* 2001;251(2):85-89. doi: 10.1007/s004060170057
10. Broderick JE, Junghaenel DU, Schneider S, et al. Pittsburgh and Epworth sleep scale items: accuracy of ratings across different reporting periods. *Behav Sleep Med* 2013;11(3):173-88. doi: 10.1080/15402002.2012.654549 [published Online First: 2012/12/05]
11. Patel S, Kon SSC, Nolan CM, et al. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. *Am J Respir Crit Care Med* 2018;197(7):961-63. doi: 10.1164/rccm.201704-0672LE [published Online First: 2017/09/30]
12. Oral Presentation 32: Thresholds for Clinically Meaningful Changes on the Epworth Sleepiness Scale and Maintenance of Wakefulness Test Sleep Latency World Sleep 2019; 2019 20 - 25 September 2019; Vancouver, Canada.
13. Scrima L, Emsellem HA, Becker PM, et al. Identifying clinically important difference on the Epworth Sleepiness Scale: results from a narcolepsy clinical trial of JZP-110. *Sleep medicine* 2017;38:108-12. doi: 10.1016/j.sleep.2017.07.006 [published Online First: 2017/10/17]
14. Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol* 1982;53(6):658-61. [published Online First: 1982/06/01]
15. Doghramji K, Mitler MM, Sangal RB, et al. A normative study of the maintenance of wakefulness test (MWT). *Electroencephalogr Clin Neurophysiol* 1997;103(5):554-62. [published Online First: 1997/12/24]
16. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28(1):113-21. doi: 10.1093/sleep/28.1.113 [published Online First: 2005/02/11]
17. Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol* 2019;85(3):359-70. doi: 10.1002/ana.25423 [published Online First: 2019/01/30]

18. Carter LP, Henningfield JE, Wang YG, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the human abuse liability of solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor. *J Psychopharmacol* 2018;32(12):1351-61. doi: 10.1177/0269881118796814 [published Online First: 2018/10/03]
19. Jazz Pharmaceuticals. **CONFIDENTIAL.** TONES 2 Clinical study report. A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy. , 2017.
20. Ruoff C, Swick TJ, Doekel R, et al. Effect of Oral JZP-110 (ADX-N05) on Wakefulness and Sleepiness in Adults with Narcolepsy: A Phase 2b Study. *Sleep* 2016;39(7):1379-87. doi: 10.5665/sleep.5968 [published Online First: 2016/05/12]
21. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurol* 2013;12(11):1068-75. doi: 10.1016/s1474-4422(13)70225-4
22. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2017;16(3):200-07. doi: 10.1016/S1474-4422(16)30333-7
23. US Xyrem® Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep* 2002;25(1):42-9. [published Online First: 2002/02/09]
24. Bogan RK, Roth T, Schwartz J, et al. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2015;11(4):427-32. doi: 10.5664/jcsm.4598 [published Online First: 2015/01/13]
25. Xyrem® International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2005;1(4):391-97.
26. Xyrem® International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep medicine* 2005;6(5):415-21. doi: 10.1016/j.sleep.2005.03.010 [published Online First: 2005/08/16]
27. Bogan RK, Swick T, Mamelak M, et al. Evaluation of quality of life in patients with narcolepsy treated with sodium oxybate: use of the 36-Item Short-Form health survey in a clinical trial. *Neurology and therapy* 2016;5(2):203-13. doi: 10.1007/s40120-016-0053-5
28. Weaver T, Cuellar N. A randomized trial evaluating the effectiveness of sodium oxybate therapy on quality of life in narcolepsy. *Sleep* 2006;29(9):1189-94.
29. Black J, Houghton W. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep* 2006;29(7):939-46.
30. Golicki D, Bala MM, Niewada M, et al. Modafinil for narcolepsy: systematic review and meta-analysis. *Medical science monitor : international medical journal of experimental and clinical research* 2010;16(8):Ra177-86. [published Online First: 2010/07/31]
31. Lehert P, Falissard B. Multiple treatment comparison in narcolepsy: a network meta-analysis. *Sleep* 2018;41(12) doi: 10.1093/sleep/zsy185 [published Online First: 2018/09/22]
32. Billiard M, Besset A, Montplaisir J, et al. Modafinil: a double-blind multicentric study. *Sleep* 1994;17(8 Suppl):S107-12. doi: 10.1093/sleep/17.suppl_8.s107 [published Online First: 1994/12/01]

33. Boivin DB, Montplaisir J, Petit D, et al. Effects of modafinil on symptomatology of human narcolepsy. *Clin Neuropharmacol* 1993;16(1):46-53. doi: 10.1097/00002826-199302000-00005 [published Online First: 1993/02/01]
34. Broughton RJ, Fleming JA, George CF, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997;49(2):444-51. doi: 10.1212/wnl.49.2.444 [published Online First: 1997/08/01]
35. Saletu MT, Anderer P, Saletu-Zyhlarz GM, et al. EEG-mapping differences between narcolepsy patients and controls and subsequent double-blind, placebo-controlled studies with modafinil. *Eur Arch Psychiatry Clin Neurosci* 2005;255(1):20-32. doi: 10.1007/s00406-004-0530-1 [published Online First: 2004/11/13]
36. Kollb-Sielecka M, Demolis P, Emmerich J, et al. The European Medicines Agency review of pitolisant for treatment of narcolepsy: summary of the scientific assessment by the Committee for Medicinal Products for Human Use. *Sleep medicine* 2017;33:125-29. doi: 10.1016/j.sleep.2017.01.002 [published Online First: 2017/04/30]
37. Donegan S, Williamson P, Gamble C, et al. Indirect comparisons: a review of reporting and methodological quality. *PloS one* 2010;5(11):e11054. doi: 10.1371/journal.pone.0011054 [published Online First: 2010/11/19]
38. European Medicines Agency. Assessment Report: Wakix (pitolisant). London, 2015.
39. Snedecor SJ, Mayer G, Thorpy MJ, et al. Multiple treatment comparison in narcolepsy: a network meta-analysis-methodological concerns. *Sleep* 2019;42(5) doi: 10.1093/sleep/zsz024 [published Online First: 2019/05/16]
40. Stevens JW. A note on dealing with missing standard errors in meta-analyses of continuous outcome measures in WinBUGS. *Pharmaceutical statistics* 2011;10(4):374-8. doi: 10.1002/pst.491 [published Online First: 2011/03/12]
41. Dias S, Welton N.J., Sutton A.J., Ades A.E. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials 2011 [Available from: http://nicedsu.org.uk/wp-content/uploads/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf accessed 7 January 2020.
42. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials (last updated April 2014): Decision Support Unit, 2011.
43. Owen RK, Bradbury N, Xin Y, et al. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Research synthesis methods* 2019;10(4):569-81. doi: 10.1002/jrsm.1373 [published Online First: 2019/07/28]
44. Lanting L, Roome C, Lang L, et al. Sodium oxybate for narcolepsy with cataplexy - A cost-effective analysis. *Journal of Neuroinfectious Diseases* 2014;5:2.
45. McDaid C, Griffin S, Weatherly H, et al. NICE TA139 Assessment report: The Continuous Positive Airway Pressure for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. 2007
46. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Medical Decision Making* 2006;26(4):410-20.
47. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2008;11(7):1131-43. doi: 10.1111/j.1524-4733.2008.00352.x [published Online First: 2008/05/21]
48. Teixeira VG, Faccenda JF, Douglas NJ. Functional status in patients with narcolepsy. *Sleep medicine* 2004;5(5):477-83. doi: 10.1016/j.sleep.2004.07.001 [published Online First: 2004/09/03]
49. National Institute for Health and Care Excellence. Obstructive sleep apnoea syndrome, Clinical Knowledge Summary 2015 [Available from:

https://cks.nice.org.uk/obstructive-sleep-apnoea-syndrome#!diagnosisAdditional accessed 10 December 2019.
50. Billiard M, Dauvilliers Y, Dolenc-Grošelj L, et al. Ch 38. Management of Narcolepsy in Adults. In: Gilus N, Barnes M, Brainin M, eds. European Handbook of Neurological Management. 2nd ed. Chichester, West Sussex, United Kingdom: John Wiley & Sons 2011:513-28.
51. Office of National Statistics. National Life Tables, 2015-2017 2018 [Available from: https://www.ons.gov.uk/releases/nationallifetablesuk2015to2017 accessed 7 January 2020.
52. Ohayon MM, Black J, Lai C, et al. Increased mortality in narcolepsy. *Sleep* 2014;37(3):439-44. doi: 10.5665/sleep.3470 [published Online First: 2014/03/04]
53. Ayas NT, FitzGerald JM, Fleetham JA, et al. Cost-effectiveness of continuous positive airway pressure therapy for moderate to severe obstructive sleep apnea/hypopnea. *Arch Intern Med* 2006;166(9):977-84. doi: 10.1001/archinte.166.9.977 [published Online First: 2006/05/10]
54. Gray A, Clarke P, Wolstenholme K, et al. Applied Methods of Cost-effectiveness Analysis in Healthcare. Handbooks in Health Economic Evaluation, volume 3. 2010.
55. Thorpy MJ BR. Update on the pharmacologic management of narcolepsy: mechanisms of action and clinical implications. *Sleep medicine* 2020 doi: https://doi.org/10.1016/j.sleep.2019.09.001
56. Malhotra A, Shapiro C, Pepin JL, et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. *Sleep* 2019 doi: 10.1093/sleep/zsz220 [published Online First: 2019/11/07]
57. Dauvilliers Y, Beziat S, Pesenti C, et al. Measurement of narcolepsy symptoms: the Narcolepsy Severity Scale. *Neurology* 2017;88(14):1358-65. doi: 10.1212/wnl.0000000000003787 [published Online First: 2017/03/05]
58. Dodel R, Peter H, Spottke A, et al. Health-related quality of life in patients with narcolepsy. *Sleep medicine* 2007;8(7-8):733-41. doi: http://dx.doi.org/10.1016/j.sleep.2006.10.010
59. Govi A, Gnucci V, Vignatelli L, et al. A pragmatic approach to test the reliability of a classification of permanent impairment due to narcolepsy. *Journal of Sleep Research Conference: 23rd Congress of the European Sleep Research Society, ESRS* 2016;25(Supplement 1) doi: http://dx.doi.org/10.1111/jsr.12446
60. Ingravallo F, Gnucci V, Pizza F, et al. The burden of narcolepsy with cataplexy: how disease history and clinical features influence socio-economic outcomes. *Sleep medicine* 2012;13(10):1293-300. doi: 10.1016/j.sleep.2012.08.002 [published Online First: 2012/10/03]
61. Dolan P, Gudex C, Kind P, et al. A Social Tariff for Euroqol: Results From a UK General Population Survey. *York: University of York Centre for Health Economics* 1995
62. Bolin K, Berling P, Wasling P, et al. The cost-utility of sodium oxybate as narcolepsy treatment. *Acta Neurologica Scandinavica* 2017;136(6):715-20. doi: http://dx.doi.org/10.1111/ane.12794
63. Flores NM, Villa KF, Black J, et al. The humanistic and economic burden of narcolepsy. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2016;12(3):401-7. doi: 10.5664/jcsm.5594 [published Online First: 2015/11/01]
64. Ara R, Brazier J, Zouraq IA. The Use of Health State Utility Values in Decision Models. *PharmacoEconomics* 2017;35(1):77-88. doi: 10.1007/s40273-017-0550-0
65. van den Berg B. SF-6D population norms. *Health Economics* 2012;21(12):1508-12. doi: 10.1002/hec.1823
66. Villa KF, Black J, Chervin R, et al. Humanistic burden of narcolepsy: Results from the national health and wellness survey. *Sleep Conference: 29th Annual Meeting of the Associated Professional Sleep Societies, LLC, SLEEP* 2015;38(SUPPL. 1)

67. Hayduk R, Mitler M. Sodium oxybate therapy improves the quality of life of narcolepsy patients. *Sleep* 2001:A328.
68. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *Journal of health economics* 2002;21(2):271-92. [published Online First: 2002/04/10]
69. NICE. NICE DSU Technical support document 10: The use of mapping methods to estimate health state utility values [Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD-10-mapping-FINAL.pdf accessed 13/03/2020.
70. National Health Service. National Drug Tariff 2019 [Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff accessed 7 January 2020.
71. National Institute for Health and Care Excellence. Narcolepsy with or without cataplexy in adults: pitolisant. Evidence summary [ES8] 2017 [Available from: https://www.nice.org.uk/advice/es8/resources/narcolepsy-with-or-without-cataplexy-in-adults-pitolisant-pdf-32181397189 accessed 7 January 2020.
72. EMC. Pitolisant SmPC [Available from: https://www.medicines.org.uk/emc/medicine/32397 accessed 13/03/2020.
73. NHS. Shared care prescribing guideline [Available from: http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Shared%20Care%20Protocols/Shared%20Care%20Prescribing%20Guidelines%20Cataplexy%20Narcolepsy%20Aug%2018.pdf accessed 13/03/2020.
74. Hospital and Community Health Services. Hospital and Community Health Services (HCHS) pay and price inflation [Available from: https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=2ahUKEwiVudX3lNvfAhUJShUIHSBBBUAQFjABegQICBAC&url=http%3A%2F%2Fwww.info.doh.gov.uk%2Fdoh%2Ffinman.nsf%2Faf3d43e36a4c8f8500256722005b77f8%2F360a47827991d10a80258036002d8d9f%2F%24FILE%2F2015.16%2520Pay%2520%26%2520Price%2520series.xlsx&usg=AOvVaw0Ny2teATbwmkIyuljThctL accessed 13/03/2020.
75. Dodel R, Peter H, Walbert T, et al. The socioeconomic impact of narcolepsy. *Sleep* 2004;27(6):1123-28.
76. NHS. National Cost Collection for the NHS, [Available from: https://improvement.nhs.uk/resources/national-cost-collection/ accessed 13/03/2020.
77. NHS. 2017/18 Reference Costs [Available from: https://improvement.nhs.uk/resources/reference-costs/#rc1718 accessed 13/03/2020.
78. Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. *Sleep* 2009;32(7):915-9. doi: 10.1093/sleep/32.7.915 [published Online First: 2009/07/31]
79. Jenkinson C, Stewart-Brown S, Petersen S, et al. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health* 1999;53(1):46-50. doi: 10.1136/jech.53.1.46 [published Online First: 1999/05/18]
80. The EuroQol Group. EQ-5D-5L User Guide. Version 3.0 2019 [Available from: https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf accessed 7 January 2020.
81. Reilly MC. Work Productivity and Activity Impairment Questionnaire scoring 1993 [Available from: http://www.reillyassociates.net/WPAI_Scoring.html accessed 7 January 2020.
82. Reilly MC. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) 1993 [Available from: http://www.reillyassociates.net/WPAI_SHP.html accessed 7 January 2020.

83. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4(5):353-65. doi: 10.2165/00019053-199304050-00006 [published Online First: 1993/10/05]
84. Efthimiou O. Practical guide to the meta-analysis of rare events. *Evidence-based mental health* 2018;21(2):72-76. doi: 10.1136/eb-2018-102911 [published Online First: 2018/04/14]
85. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Statistics in medicine* 2007;26(1):53-77. doi: 10.1002/sim.2528 [published Online First: 2006/04/06]
86. EMA. Sodium oxybate SmPC [Available from: https://www.ema.europa.eu/en/documents/product-information/xyrem-epar-product-information_en.pdf accessed 13/03/2020.
87. EMC. Dexamfetamine SmPC [Available from: https://www.medicines.org.uk/emc/product/11004/smpc accessed 13/03/2020.
88. British National Formulary. Pitolisant 2019 [updated 16th August 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/pitolisant.html accessed 7 January 2020.
89. British National Formulary. Sodium Oxybate 2019 [Available from: https://bnf.nice.org.uk/medicinal-forms/sodium-oxybate.html accessed 7 January 2020.

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**).

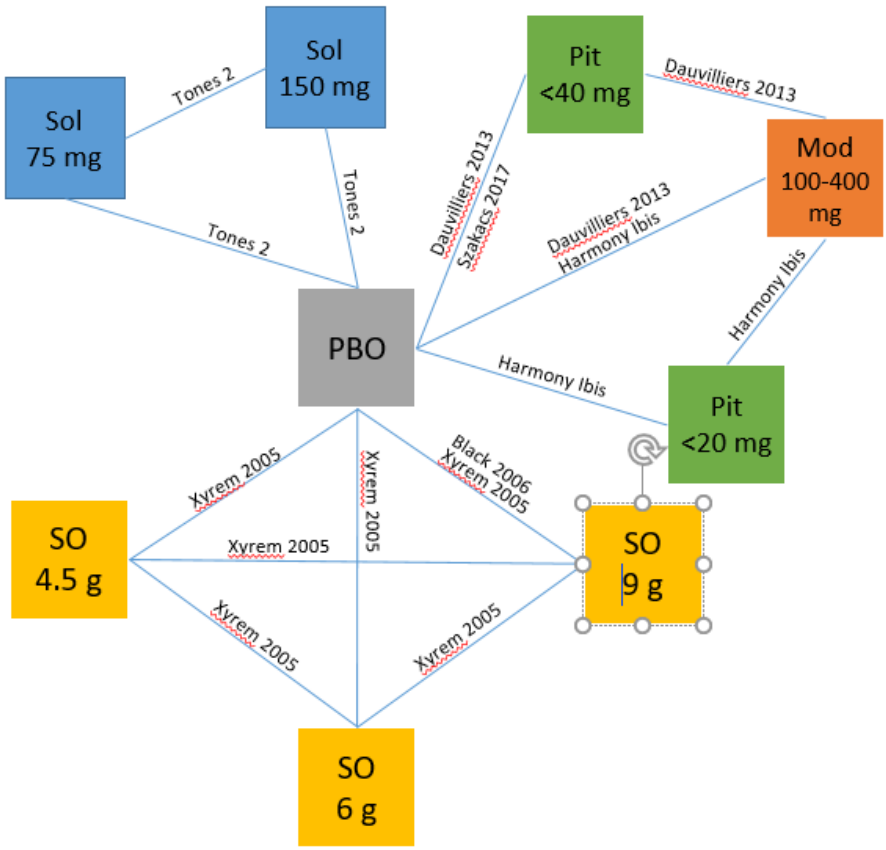


Figure 12 ESS 8-week NMA scenario: impact of separating pitolisant doses

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.** **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	?	

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

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

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 25 March 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Unnecessary CIC mark up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, paragraph 1 CIC mark up on a "…statistically significant mean difference in ESS relative to placebo occurred only for the 150mg solriamfetol dose at this time point."	CIC mark-up can be removed	Data is in the public domain (Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3):359-70.)	Thank you. The CIC mark-up has been removed.

Issue 2 Potentially misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16, paragraph 2 "Healthcare resource use (including doctor appointments and hospitalisation due to serious AEs) reported in TONES 5 CSR was [redacted] in patients treated with solriamfetol 150 mg compared to solriamfetol 75 mg dose. However, these costs are not included in the company's analysis. "	"Healthcare resource use collected as an exploratory outcome (including doctor appointments and hospitalisation due to serious AEs) reported in TONES 5 CSR showed a possible trend towards [redacted] utilisation in patients treated with solriamfetol 150 mg compared to solriamfetol 75 mg dose in many instances. However, these costs are not included in the company's analysis. "	This is a potentially misleading statement given the exploratory nature of the analysis, the low patient numbers available for analysis, the lack of data available on the narcolepsy subset specifically and the variability observed across all three solriamfetol doses employed in the trial (including the unlicensed 300 mg dose). The statement should be presented in a more balanced way to highlight the uncertainty in the data presented.	This is not factual inaccuracy, but we agree that there is substantial uncertainty in the healthcare resource use due to a relatively small number of patients in TONES 5, and the lack of narcolepsy-specific estimates. We note in the TONES 5 CSR page 6 that the economic outcomes, namely the mean/median healthcare costs over the 1-year period were planned outcomes in this trial. We have updated the ERG report based on this

			information and suggested amendments.

Issue 3 Data correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20, paragraph 1 “The CS estimates that 20%-60% of patients may not respond to first line modafinil. “	“The CS estimates that 20%-66% of patients may not respond to first line modafinil.”	Correct data in line with CS page 23	This typographical error has been corrected.

Issue 4 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, paragraph 2 "...or 52 weeks if they had enrolled with a break after historical participation in a previous study (Group B)”	“…or 52 weeks if they had enrolled after historical participation in a previous study after which they may have had a break (Group B)”	Patients in Group B may have had a break although this may not have been the case for all patients	The text on CS B.2.4.3.3 p.62 which describes TONES 5 patients suggests there was a break for all patients, albeit only ‘days’ for some. Nevertheless we have altered the wording as suggested (and also amended similar wording in the footnote to Table 8 and in Appendix 1).

Issue 5 Unnecessary CIC mark-up

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Table 11, page 42
Effects of solriamfetol on change in ESS compared to placebo at week 8
<table>
<tr><th>Secondary outcome</th><th>Placebo (N=58)</th><th>Solriamfetol 75mg (N=59)</th><th>Solriamfetol 150mg (N=55)</th></tr>
<tr><td colspan="4">Change in ESS from baseline at 8 weeks</td></tr>
<tr><td>LS mean (SE)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean difference (95% CI, p-value) relative to placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>CIC mark-up on specific values can be removed as shown below
<table>
<tr><th>Secondary outcome</th><th>Placebo (N=58)</th><th>Solriamfetol 75mg (N=59)</th><th>Solriamfetol 150mg (N=55)</th></tr>
<tr><td colspan="4">Change in ESS from baseline at 8 weeks</td></tr>
<tr><td>LS mean (SE)</td><td>-2.1([redacted])</td><td>-3.4 ([redacted])</td><td>-5.2 ([redacted])</td></tr>
<tr><td>Mean difference (95% CI, p-value) relative to placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>-2.1, -3.4 and -5.2 are available in the public domain (Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3):359-70.)</td>
<td>We have removed the CIC mark-up from the specific values shown and also amended the source to include the Thorpy et. al. paper.</td>
</tr>
</table>

Issue 6 Potentially misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 16, page 501 In TONES 5 (CSR Table 14.3.1.19.2), [redacted] in the narcolepsy sub-population experienced an event classified within an event cluster defined as 'Depression and Suicidality'[a]; all doses combined).	"In TONES 5 (CSR Table 14.3.1.19.2), [redacted] receiving solriamfetol 75mg and 150mg in the narcolepsy sub-population experienced an event classified within an event cluster defined as 'Depression and Suicidality'[a])."	[redacted] includes the unlicensed 300 mg dose and hence the value is not representative of the rate that may be seen in practice with licensed doses (75 and 150mg).	This is not a factual error. We have indicated that the data are for all doses combined (and note that the safety population for TONES 5 was all patients who received ≥1 dose of study drug). Nevertheless we have amended the text to provide the reader with information for the 75mg and 150mg solriamfetol dose groups.

Issue 7 Potentially misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 16 page 50 "Palpitations were reported more frequently for solriamfetol 150mg (6.8%) versus placebo (2.0%) in TONES 1."	"Palpitations were reported more frequently for solriamfetol 150mg (6.8%) versus placebo (2.0%) in TONES 1, although number of patients experiencing these events was low (n=3 and 1, respectively). Similarly the number of palpitation AEs reported in TONES 2 and TONES 5 with solriamfetol were low (n≤2). (Source: TONES 2 data CS page 116; TONES 5 data CSR Table 14.3.1.19.2)"	To provide a more balanced assessment for this AE.	Not a factual inaccuracy. Nevertheless the ERG has amended the text to indicate numbers of patients involved for TONES 1 and added text for TONES 2.

Issue 8 Data correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96, paragraph 1 "The mean baseline EQ-5D index score in TONES 2 (n=172, mITT population) was [redacted]	"The mean baseline EQ-5D index score in TONES 2 across all solriamfetol dose groups (n=172, mITT population) was [redacted]	Mean baseline EQ-5D index score across the entire TONES 2 trial doesn't appear to be available in CSR Table 14.2.10.1, but is available as a mean value across all solriamfetol dose groups. For this group the baseline index score is [redacted] as the ERG state. In addition, 95% CI were not provided in the CSR table cited. Corrected text has been provided.	Amendment made as requested, and we have also added results for the placebo group ([redacted]).

Issue 9 Text correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 100, paragraph 2 "The results are reported in CS Table 6.14."	"The results are presented in CS Table 42."	Incorrect table number cited.	Corrected.

Issue 10 Potentially misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106, paragraph 1 "As clearly seen from [redacted] (Appendix 9), the estimated healthcare cost was [redacted] 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). "	"As seen from [redacted] (Appendix 9), there was a possible trend towards [redacted] estimated healthcare cost 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). "	This is a potentially misleading statement given the exploratory nature of the analysis, the low patient numbers available for analysis, the lack of data available on the narcolepsy subset specifically and the variability observed across all three solriamfetol doses employed in the trial (including the unlicensed 300 mg dose). The statement should be presented in a more balanced way to highlight the uncertainty in the data presented.	See response to Issue 2. We have revised the text as suggested (pages 107 and 110).

Issue 11 Potentially misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107 [redacted] The respective proportions of patients hospitalised due to SAEs in TONES 5 (assuming one	[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	There is large degree of uncertainty in these data which make the assumption of [redacted] hospitalisation subject to uncertainty. 1. The n number for the 75mg dose is only 15 such that the sample size for capturing the incidence of an SAE	This is not factual inaccuracy. We agree, however, that the number of patients in TONES 5 was relatively low and, therefore, the estimates are uncertain.

hospitalisation per patient) are [redacted]% and [redacted]% per [redacted] weeks (the weighted average duration of follow-up across groups A and B, see [redacted]). Hence, it appears that hospitalisation in TONES 5 participants was [redacted].”	[redacted]). Hence, it could be postulated that hospitalisation in TONES 5 participants was [redacted], although is subject to uncertainty due to small sample size.”	requiring hospitalisation is probably inadequate to allow conclusions of a [redacted] in SAE rates 2. The occurrence of only a single SAE in TONES 2 supports this and highlights the uncertainty associated with assuming a [redacted] in hospitalisation due to SAE. The statement should be presented in a more balanced way to highlight the uncertainty in the data presented.	We have updated the ERG report accordingly.

Issue 12 Statement incomplete

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 114, paragraph 3 “The cost-effectiveness results for various doses of methylphenidate (from 18 mg to 72 mg) against solriamfetol 75 mg and 150 mg were obtained for a range of ΔESS relative to solriamfetol (from -7 to -1) (see CS Tables 79-80).”	“The cost-effectiveness results for various doses of methylphenidate (from 18 mg to 72 mg for modified release tablets and from 10 mg to 60 mg for modified release 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).”	The CS presented analyses for methylphenidate modified release tablets and capsules. The suggested amendment reflects the full analyses provided in the CS.	We have amended the text to note that results are presented for a range of methylphenidate MR tablet and capsule doses.

Issue 13 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 39, page 117 ERG report corrections to the company model with regard list prices for dexamphetamine and methylphenidate.	Wording should be added to clarify that this isn't a correction to an error by the company but rather the ERG opinion that an alternative price source is more appropriate.	The company used the Drug Tariff as the source of costs for dexamphetamine and methylphenidate, reflecting prices available in Primary Care. If there are shared care agreements in place and therefore prescribing is continued in primary care – which isn't unrealistic given the limited number of hospitals treating narcolepsy – then the costs incurred would be those quoted in the drug tariff. In contrast the prices quoted by the ERG are eMIT prices that are available to hospitals only. The reality is that the prices are likely to be somewhere between the two sources.	This is not a factual inaccuracy. In our critique of the company's submission, we used the lowest unit costs for the drugs in question from the current official listing published by the Department of Health. To our knowledge, doses of dexamfetamine over 30mg are restricted to secondary care prescribing and monitoring only: http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2014/01/Dexamfetamine-for-primary-sleep-disorder-primary-care-info-Nov-2013.pdf Since the average dose of dexamfetamine modelled by the company is 40 mg per day, the ERG analysis was based on unit costs from eMIT. No changes made.

Issue 14 Data correction

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>HARMONY IBIS inputs provided by ERG:
<table>
<tr><td>ARM</td><td>N</td><td>SD</td><td>ESS mean change</td><td>SE</td></tr>
<tr><td>Placebo</td><td>32</td><td>5.6</td><td>-3.6</td><td>0.990</td></tr>
<tr><td>Pitolisant ≤40mg</td><td>66</td><td>4.6</td><td>-4.6</td><td>0.566</td></tr>
<tr><td>Modafinil</td><td>65</td><td>5.9</td><td>-7.8</td><td>0.732</td></tr>
</table>
</td>
<td>The inputs used for the HARMONY IBIS trial have a different N value than those reported in the summary of product characteristics for pitolisant. Based on these N values, the SE for the HARMONY IBIS ESS results are shown below:
<table>
<tr><td>ARM</td><td>N</td><td>SD</td><td>ESS mean change</td><td>SE</td></tr>
<tr><td>Placebo</td><td>33</td><td>5.6</td><td>-3.6</td><td>0.975</td></tr>
<tr><td>Pitolisant ≤ 40 mg</td><td>67</td><td>4.6</td><td>-4.6</td><td>0.562</td></tr>
<tr><td>Modafinil</td><td>65</td><td>5.9</td><td>-7.8</td><td>0.732</td></tr>
</table>
</td>
<td>Correction for technical accuracy.</td>
<td>No correction required, the ERG has used the ITT values for each trial as indicated in the header for the Table of ERG corrected ESS-8 week NMA input data in Appendix 6. Harmony IBIS ITT values from EPAR Table 12.</td>
</tr>
</table>

Issue 15 Text correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
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	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 include in cost-effectiveness analysis solreiamfetol is not cost-	Correction of name of medicine from sodium oxybate to methylphenidate.	Thank you, corrections made.

that when dexamfetamine and sodium oxybate are include in cost-effectiveness analysis solreiamfetol is not cost-effective at the £20,000 per QALY threshold. However, comparative clinical effectiveness evidence is lacking for dexamfetamine and sodium oxybate.	effective at the £20,000 per QALY threshold. However, comparative clinical effectiveness evidence is lacking for dexamfetamine and methylphenidate.		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Solriamfetol for treating excessive waketime sleepiness caused by narcolepsy

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Key abbreviations used:
EDS: Excessive daytime sleepiness
ESS: Epworth Sleepiness Scale

Issue	Summary	Technical Team Preliminary Judgement
1. Treatment pathway	Solriamfetol has a marketing authorisation "to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy)." The **company** have positioned solriamfetol as a treatment option after treatment with modafinil, as it considers modafinil to be established first line treatment. The **ERG** stated that clinical advice received from its clinical experts supports the continued use of modafinil as a first-line treatment and the positioning of solriamfetol as a second-line treatment option. It noted that the company did not model any further lines of treatment after second line. A submission from a professional group (**Association of British Neurologists**) stated that solriamfetol may be considered as a third or fourth-line treatment option (depending on patient characteristics and co-morbidities).	The marketing authorisation for solriamfetol does not restrict its use to a specific line of treatment in the clinical pathway. Modafinil is considered an established first line treatment in NHS clinical practice and the company's positioning of solriamfetol as a treatment option after modafinil appears to be appropriate. However, it is unclear whether solriamfetol would only be used as a second-line treatment. The technical team considers that: • Clinical advice is needed on the likely positioning of solriamfetol in the clinical pathway. • Clinical advice is needed on what proportion of people receive subsequent treatments after first-line therapy, and which treatments are used. • The company should provide alternative scenarios for comparisons of solriamfetol with third and fourth line treatments. • The company should provide a scenario in which further lines of treatment are

		modelled after solriamfetol and the comparator treatments at second-line. • Clinical advice is needed on whether the treatment pathway differs for people with cataplexy.
2. Comparators	The final scope issued by NICE specifies the following comparators: • modafinil • dexamfetamine • methylphenidate • sodium oxybate • pitolisant As the **company** considered solriamfetol as a treatment option following modafinil (see issue 1), it did not consider modafinil to be a comparator. The **company** stated that there is no comparative trial evidence for dexamfetamine and methylphenidate, therefore these treatments are only included in scenario analyses. It highlighted that these treatments have an estimated market share of 17.4% and 2.7% respectively, which is declining. Therefore, the company provided cost-effectiveness results for solriamfetol compared with pitolisant and sodium oxybate only in its base case. The **ERG** considered that modafinil was not a comparator because of the company's positioning of solriamfetol after modafinil in the treatment pathway. The ERG stated that this is reasonable. The ERG considered that comparing solriamfetol with dexamfetamine and methylphenidate in scenario analyses was appropriate	The technical team considers that the position of solriamfetol within the treatment pathway informs the choice of most appropriate comparator treatments (see issue 1). The technical team also considers that the estimated market share for dexamfetamine (17.4%) is significant and therefore should be included within base case analysis (fully incremental). The technical team considers that: • Clinical advice is needed on what proportion of patients receive pitolisant, sodium oxybate, dexamfetamine, methylphenidate and antidepressants, and in what position in the treatment pathway. • Clinical advice is needed on whether dexamfetamine should be included in base case analysis rather than scenario analysis? • Clinical advice is needed on what influences the choice of treatment with pitolisant, sodium oxybate, dexamfetamine, methylphenidate, antidepressants and solriamfetol. • Clinical advice is needed to determine if the presence of cataplexy impacts on which treatments are used?

	as there is a lack of suitable clinical data for these treatments, although they noted that these drugs have a low acquisition cost. Expert clinical advice given to the ERG stated that prescribing practice may vary between clinicians according to preference and local prescribing guidance. A submission from a professional group **(Association of British Neurologists)** suggested that dexamfetamine and methylphenidate are usually given as a second line treatments and in some cases sodium oxybate may not be accessible across different regions in the NHS in England. It also suggested that cataplexy is treated with different antidepressants. When compared with dexamfetamine and methylphenidate, solriamfetol is not considered cost-effective at a £20,000 per QALY gained threshold. However, these comparisons are based on assumed reductions in ESS relative to solriamfetol because of the lack of clinical effectiveness evidence for these treatments.	
3. Generalisability of the clinical trial evidence	The clinical evidence for solriamfetol comes from 3 clinical trials: TONES 2, TONES 5 and TONES 1. The treatment effect for solriamfetol is estimated using individual patient data from TONES 2, with supportive evidence for modelling assumptions related to treatment effect provided by TONES 5 and TONES 1. The **ERG** considered that in general the trial population appeared to align with the company's decision problem (people with excessive daytime sleepiness for whom	The technical team notes that the TONES 2 trial is the only clinical evidence source used to inform the treatment effect of solriamfetol in the model. Therefore, it is important that the population enrolled in this trial is generalisable to people with excessive daytime sleepiness caused by narcolepsy. The technical team considers that: • Clinical advice is needed on whether people recruited to TONES 2 are

	earlier treatment may have been unsuitable or inadequate). It noted that there was some uncertainty around the representativeness of the clinical trial populations to those seen in NHS clinical practice (table 5 page 29 ERG report and company submission section B.2.3.2 Tables 7, 9 and 10). It also noted that there was limited information on the demographics of people with narcolepsy in England and that the clinical trials were predominantly based in the United States and Canada. The **ERG** highlighted that the trial population had a higher proportion of women, tended to be younger and a lower proportion with cataplexy (~50% in the trial) than would be expected in NHS clinical practice in England (In the company submission it is estimated that ~70% of people with narcolepsy also have cataplexy, clinical advice given to the ERG suggests that the figure is between 50% to 87.5%). The **company** highlighted that the lower than expected proportion of people with cataplexy in the clinical trials was likely a result of the small sample sizes and that some may not have wished to stop their anti-cataplexy medication (which was a requirement for entering the trial). The **ERG** noted that the company used the baseline characteristics of a modified intention to treat (mITT) population of the 150 mg solfriamfetol arm of TONES 2 in the analysis (received ≥1 dose of study drug and had a baseline and ≥1 post-baseline evaluation of ESS or MWT). The **ERG** considered that the use of a mITT population excludes ~3% of the trial population of TONES 2, therefore any bias is likely to be small. The **ERG** preferred to use baseline characteristics from the full eligible population recruited to the pivotal trial,	reflective of those seen in clinical practice in regard to baseline characteristics such as ESS score, previous treatments and proportion of people with cataplexy.

	regardless of allocated treatment arm (see ERG report table 26, page 85). It noted this change makes only minor changes to the cost-effectiveness results.	
4. Indirect treatment comparison (ITC)	As there were no clinical trials which directly compared solriamfetol with the comparators listed in the final scope issued by NICE, the company did an indirect treatment comparison (ITC) using network meta-analysis. The **company** did 12 separate NMAs, each linking treatments through a common comparator (placebo), 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 because of TEAEs). 7 clinical trials met the inclusion criteria for the NMAs but every trial did not report measures for each of the outcomes. Therefore, the number of clinical trials informing each NMA varied (between 2 to 6). No evidence was identified for the comparators, dexamfetamine or methylphenidate for the NMAs. The **company** preferred the use of a fixed-effects model for the NMA analysis. In the company's NMA analysis, solriamfetol 150 mg provided a greater reduction in ESS score relative to placebo, solriamfetol 75 mg and sodium oxybate 4.5 mg (95% credibility intervals do not cross zero). This dose (150 mg) also provided a numerical ESS improvement over sodium oxybate 6 mg (95% credibility interval crosses zero) but did not provide a numerical improvement relative to sodium oxybate 9 mg or pitolisant <40 mg (credible intervals crosses zero). The **ERG** noted that the primary aim of the clinical trials included in the NMAs varies between treating excessive	The technical team acknowledges there is uncertainty in the results from the indirect treatment comparison because of the small numbers of clinical trials and the use of imputation to calculate standard errors. The technical team accepts that the degree of heterogeneity does not prevent the use of an NMA in this appraisal and considers that the analysis based on the random effects model are likely to be more appropriate. The technical team also agree with the ERG's inclusion of the Harmony Ibis and modafinil data from Harmony Ibis and the Dauvilliers (2013) trials. The technical team considers that clinical advice is needed on: • whether cataplexy and the related use of concomitant medication are potential treatment effect modifiers and to what extend this may add to the uncertainty in the indirect treatment comparison. • the external validity of the results from the company's and ERG's indirect treatment comparison (i.e. are results as expected?). • The appropriateness of including the Harmony Ibis trial including its modafinil treatment arms and the modafinil treatment arms of the included Dauvilliers

	daytime sleepiness or cataplexy. It highlighted that the proportion of people with cataplexy varies across the trials and therefore the use of concomitant anti-cataplexy medication will also vary. It noted that the company's clinical experts had stated that cataplexy and the related use of concomitant medication were potential treatment effect modifiers. The **ERG** preferred the use of a random-effect model) for the NMA analysis because of heterogeneity in the clinical trial evidence. These produce similar estimates, however the 95% credibility intervals cross zero for every comparison. The **ERG's** analysis therefore suggests that there is more uncertainty in the results of the indirect treatment comparison compared with the **company's** fixed effects model. Some trials included in the NMA did not report standard errors and therefore values had to be imputed. The **ERG** considered the use of imputation to calculate missing standard errors introduces additional uncertainty into the analysis (particularly for sodium oxybate as no standard errors were reported for trials of this treatment). The **ERG** noted that only one NMA (ESS NMA) directly informed the efficacy of treatments in the economic model (see issue 6). The ERG highlighted that the Harmony Ibis trial had been excluded from the company NMAs as were trial data for modanfinil. The ERG stated that it considers that the Harmony Ibis (pitolisant versus modafinil versus placebo) trial should be included in the NMA analysis. The **ERG** preferred to add the Harmony Ibis trial including its modafinil treatment arms and the modafinil	(2013) trial to the NMA analysis (ERG analysis).

	treatment arms of the included Dauvilliers (2013) trial to the NMA analysis (the inclusion of the modafinil data adds to network connectivity and allows an assessment of consistency in the placebo-pitolisant-modafinil loop). The ERG considered modafinil does (100, 200 and 400 mg) separately. The ERG updated the company's NMA where possible. The ERG also updated the NMAs based on errors it had identified. The use of the results of the indirect treatment comparison in the economic evaluation showed that solriamfetol, sodium oxybate and pitolisant produced similar reductions in ESS scores and therefore similar amounts of QALYs (ESS scores mapped to EQ-5D: Company and ERG analysis). Abbreviations: ESS: Epworth Sleepiness Scale, MWT20: 20-minute Maintenance of Wakefulness Test, MWT40: 40-minute Maintenance of Wakefulness Test, SF-36 Short-Form 36-Item Health Survey, PGI c: Patient Global Impression of change, CGI c: Clinical Global Impression of change, TEAE: treatment emergent adverse event.	
5. Subgroup analysis	The **company** provided a scenario analysis which uses data from people in TONES 2 who had received modnafinil prior to treatment with solriamfetol. The **company** received clinical advice which stated that cataplexy (and the related use of concomitant medication) were potential treatment modifiers. However, the **company** also stated that as there is no evidence to suggest that solriamfetol would impact cataplexy it was not assessed in the cost-effectiveness analysis (in its response to clarification). The **company** also provided a scenario analysis which excludes trials in which use of concomitant treatment was allowed for the comparison against sodium oxybate.	The technical team note that the subgroup analysis of people in TONES 2 who previously had treatment with modafinil matches the population for which the company have positioned solfriamfetol (see issue 1), and therefore is a relevant analysis for decision-making. The technical team considers that: • Clinical advice is needed on the robustness of the data from the subgroup of people who had received previous treatment with modafinil.

	The **ERG** noted that ~ 50% of those in TONES 2 had previously had modafinil, but that no data were collected on whether this was as a first-line treatment or why some people did not have modafinil prior to solriamfetol. The **ERG** stated that this subgroup analysis is useful, as it reflects the company's positioning of solriamfetol within the treatment pathway (see issue 1). However, the **ERG** also highlighted that this subgroup analysis is subject to uncertainty because it is based on a smaller subset of data of people receiving 150mg solriamfetol in TONES 2 (n=[redacted]), which may not be robust. The **ERG** considered the company's rationale for not providing cost-effectiveness analysis by cataplexy status to be reasonable. The **ERG** agreed with the company that the scenario which excluded use of concomitant treatments (includes only one sodium oxybate trial) means that it is not possible to make a clear judgement on the true impact of concomitant stimulant therapies in the sodium oxybate trials.	• Clinical advice is needed on whether subgroup analysis for people with and without cataplexy would be appropriate and on whether comparator treatments would also have an effect on cataplexy symptoms?
6. Estimation of the treatment effect	Excessive daytime sleepiness (EDS) caused by narcolepsy impacts quality of life of those with the condition for several reasons. The company describes the impact of excessive daytime sleepiness as having *"a substantial negative impact on the patient's ability to function psychologically, socially, and professionally"* (company submission page 16). In the economic model, the clinical effectiveness of solriamfetol and comparator drugs, is captured only	The technical team considers there to be uncertainty around the most appropriate ESS reduction threshold to use in the analysis and that the choice of threshold has the potential to alter the relative effectiveness and costs of different treatments. In addition, it is likely that there are factors considered in clinical practice other than reduction in ESS score.

	through changes in ESS from baseline (ESS values are mapped to the EQ-5D to inform QALY gains of treatments). In the **company's** base case, a response to treatment is defined as a mean ESS score reduction of 3 or more. The **ERG** considered a mean ESS reduction of 2 or more appropriate to define a response to treatment in the economic model. It provided scenario analysis for mean reductions of 3 or more and 4 or more. The threshold used for ESS reduction for response impacts on the estimated costs of the treatments in the analysis. The **ERG** noted that clinicians would likely consider additional factors beyond change in ESS score, such as impact on quality of life, when making assessment of treatment response. The ERG agreed with the company's use of reduction in mean ESS score to model treatment effectiveness given the lack of other available data. The **ERG** highlighted that while the 8-week timepoint used in the ESS NMA was reasonable (as this matched the timings in comparator trials and there is no information for ESS change at the 12-week timepoint for comparator drugs – see issue 4), it may introduce bias against sodium oxybate as this treatment may take up to 12 weeks before an improvement is seen. The **ERG** highlighted that the estimated treatment effect for solriamfetol and comparator treatments was based on a small set of individual patient level data (IPD) from TONES 2 150 mg solriamfetol dose arm. In the model, the mean ESS reduction is applied to the IPD set for	The technical team considers that clinical advice is needed: • To define what ESS reduction threshold should be used in the analysis to define response to treatment. • To ascertain factors taken into account when defining response to treatment, for example quality of life. • To comment on the timing of response assessment, and the impact of timing on the estimation of response for sodium oxybate. • To comment on the appropriateness and robustness of the company's method of applying relative mean ESS score reductions to individual level patient data from TONES 2 (which assumes the same distribution of response (ESS reduction) across all treatments.

	solriamfetol 150 mg. The relative treatment effects in terms of mean ESS reduction of other treatments (compared to 150 mg solriamfetol) are also applied to this IPD set (ERG report page 88). This method produces estimates of the proportion of people whose condition responds to each treatment option (and those whose condition doses not respond) based on which ESS score reduction threshold is used to indicate a response. It also produces estimates of the mean ESS scores for these groups (results can be seen table 25, page 79, ERG report). The method used assumes that the distributions of ESS changes are similar for the different treatments (ERG report pages 88-90). The **ERG** noted that this may not be accurate if the mechanisms of action for the treatments differ substantially.	
7. Dosing splits	Treatments for excessive sleepiness caused by narcolepsy can be administered in various doses and the proportion of people on each dose can vary across treatment options. Dose levels can also vary in cost and effectiveness. The company provided results using individual doses and combinations of doses. The various dose splits in the analysis included: • Solriamfetol (75 mg and 150 mg) • Pitolisant (18 mg and 36 mg) • Sodium oxybate (4.5 g, 6 g and 9 g) In the **company's** base case, the dose split for solriamfetol was based on use of the treatment in the United States (they assume 50% of people will be given 75mg dose and 50% given 150 mg dose). The **company** assumed, based on clinical advice it had received, that	The technical team consider that the most appropriate dosing split assumptions for solriamfetol are likely to be closer to the ERG assumptions (that is, a higher proportion of people would be given the 150 mg compared to the 75 mg dose). The technical team agrees with the ERG that combined-dose analysis is appropriate as it more closely reflects the use of these treatments in NHS clinical practice. The technical team considers that clinical advice is needed on: • The likely dose split of solriamfetol based on use of the treatment in clinical practice

	equal proportions of people who receive sodium oxybate are on 4.5 g, 6 g and 9 g doses. The company also assumed that 33.3% and 66.7% of people who received pitolisant were on 18 mg and 36 mg doses respectively. The company provided some scenario analyses for different dose splits for solriamfetol but none for the comparator drugs. The **ERG** considered that a combined-dose analysis was more relevant for decision-making as doses of treatments are usually chosen to balance effectiveness and side effects. The **ERG** considered that there was uncertainty regarding the likely dose split of the 2 solriamfetol doses. It noted that clinical advice given to the company appeared to generally support treatment being titrated to the maximum dose (150 mg) and clinical advice to the ERG stated that over 50% of people who have solriamfetol would receive the 150 mg dose. The ERG explored a base case (90% of people given 150 mg dose) and scenario analyses which varied the assumed solriamfetol dose split in a different way to the dose split used by the company. The ERG considered that the dose splits for both sodium oxybate and pitolisant in the company's base case were reasonable and the ERG provided further scenario analyses which investigated the impact of varying dose splits of these treatments.	in England, and what factors influence this. • The likely dose splits of the comparator treatments based on use of the treatments in clinical practice in England (pitolisant, sodium oxybate, dexamfetamine and methylphenidate).
8. Treatment discontinuation	The **company** assumed that long term discontinuation (after 8 weeks in the economic model) rates resulting from a lack of response or treatment emergent adverse events (TEAEs) were the same for all treatments given the lack of long term evidence informing this parameter,	The technical team considers that the following information is required: • Clinical advice is needed on the appropriateness of assumptions that treatment discontinuation resulting from a

	and were based on TONES 5 (lack of response: 10.9% and TEAEs 4.4% per year respectively). The company noted that discontinuation rates resulting from adverse events were likely to be overestimated as TONES 5 included the unlicensed 300 mg solriamfetol dose. The company explored uncertainty in these values in scenario analyses. The **company** also assumed that there was a constant ESS reduction from baseline over time for people whose disease responds to treatment (termed as "responders" in the economic model), based on clinical advice given to the company. This means that the reduction in ESS at 8 weeks after treatment was assumed to be maintained until treatment discontinuation in this group. The **ERG** considered the company's assumptions relating to treatment discontinuation resulting from adverse events to be reasonable, but that the rate may be overestimated because of TONES 5 inclusion of the unlicensed 300 mg solriamfetol dose. It also noted that scenario analyses based on the results from the ITC for discontinuation resulting from serious treatment emergent adverse events would be helpful. In addition, clinical advice to the **ERG** considered the discontinuation rate as a result of loss of response (10.9%) would be slightly lower in clinical practice. The **ERG** also considered that, given the lack of evidence on changes in narcolepsy symptoms or treatment effectiveness over time, assuming ESS response was maintained over time was reasonable.	lack of response or treatment emergent adverse events are the same across treatments (and treatment doses). • Clinical advice is needed on the appropriateness of the assumption that people whose disease responds to treatment experience a constant ESS reduction from baseline over time. • The company should provide a scenario analysis based on the results from the ITC for discontinuation resulting from serious TEAEs (as suggested by the ERG). • The company should also provide a scenario which applies a different rate of treatment discontinuation over the longer term to demonstrate the impact of this on results. Clinician input is needed on how treatment discontinuation rates may change over the longer term.

9. Resource use	The company only included drug acquisition costs in its cost effectiveness analysis. The **ERG** added costs associated with serious treatment related adverse events (table 31, page 107 ERG report) and consultant led consultations. The **ERG** noted that people whose condition did not respond to treatment were likely to be seen by clinicians (consultant-led appointments) more frequently (once every 3 months in its base case with every 6 weeks assumed in scenario analysis) than those whose condition responded to treatment (table 30 page 106, ERG report) and include these associated costs in its base case. The inclusion of these costs has the potential to change the estimated total costs for each treatment in the analysis, and therefore the cost-effectiveness estimates.	The technical team considers that the ERG approach of including other resource use costs beyond drug acquisition costs is appropriate. The technical team agrees with the ERG's assumptions regarding healthcare resource use attributed to serious treatment related adverse events and using consultant let consultation costs. In addition, the technical team agree that it is reasonable to assume that people whose disease does not respond to treatment will see clinicians more frequently than those whose condition responds to treatment. The technical team considers that clinical advice is needed on: • The frequency of healthcare appointments and how this differs depending on whether excessive daytime sleepiness has responded to treatment or not. • The frequency of healthcare appointments and how this differs depending on serious adverse events of treatment.

2 Questions for engagement

2.1 Treatment pathway

1. Is modafinil the standard first line treatment for excessive sleepiness caused by narcolepsy? Please outline the current treatment pathway for treating excessive sleepiness caused by narcolepsy. Should additional lines of treatment be modelled (the analysis currently only models 1 line of treatment after modafinil)? Does the treatment pathway differ for narcolepsy with cataplexy compared to narcolepsy without cataplexy?

2. Where in the treatment pathway is solriamfetol likely to be used? What factors influence this decision?

3. Is prior modafinil a likely treatment effect modifier for treatments given after modafinil (if yes, is this effect the same for all treatments given after modafinil)? Are other prior treatments likely to be treatment effect modifiers? Are there other factors which are likely treatment effect modifiers (such as cataplexy and containment medications) and what impact could these have on results?

2.2 Comparators

4. How often are dexamfetamine and methylphenidate used after modafinil in clinical practice? How effective are these treatments for treating excessive daytime sleepiness caused by narcolepsy? Should these treatments be included in base case analysis rather than scenario analysis? What factors influence the choice of treatments used (for example, does the presence of cataplexy impact treatment choices?).

2.3 Generalisability of the clinical trial evidence

5. How generalisable are the results from the TONES trials (particularly TONES 2) to the population seen in clinical practice?

2.4 Indirect treatment comparison

6. How robust is the indirect treatment comparison (NMA analysis)? How uncertain are the comparisons between solriamfetol and the comparator treatments? Do the results of the indirect treatment comparison, which estimates similar treatment effects (ESS score reduction), for solriamfetol, pitolisant and sodium oxybate, show face validity?

7. Do the ERG additions to the NMA make the indirect treatment analysis more robust? Is a random-effects model or fixed effect model more appropriate to use?

2.5 Subgroup analysis

8. How robust is the subgroup analysis of people who have had previous modafinil? Is this analysis more appropriate to use to inform the cost-effectiveness estimates? Would a subgroup analysis for people with and without cataplexy be appropriate? Do some of the treatments available treat cataplexy symptoms also?

2.6 Estimation of the treatment effect

9. Is the approach of using only ESS changes from baseline appropriate? Are there any other clinical outcomes which can be used to compare treatment effects?

10. What is the most appropriate ESS reduction change threshold to use in the analysis to define a response to treatment (reduction of 2 or more, 3 or more, 4 or more, or another threshold)?

11. Is the assumption of a constant treatment effect (maintained reduction in ESS from baseline) for those whose condition responds to treatment appropriate? Is it appropriate to assume the same distribution of response (ESS reduction) across all treatments?

12. Is the 8-week timepoint appropriate to capture reduction in ESS treatment effects in the NMA? Does this timepoint underestimate the likely treatment effect of sodium oxybate? If so, is this underestimation likely to be significant?

2.7 Dosing split

13. What are the most appropriate assumptions relating to the proportion of people on specific doses of each treatment in the analysis (solriamfetol, pitolisant, sodium oxybate, dexamfetamine and methylphenidate)?

14. How frequently do people change doses or treatments? What factors influence this?

2.8 Treatment discontinuation

15. Are the simplifying assumptions in the model appropriate, including the assumptions that treatment discontinuation rates (resulting from a lack of response or treatment emergent adverse events) are the same for all treatments and that ESS score reductions are constant for people whose disease responses to treatments?

2.9 Resource use

16. How appropriate is the ERG's assumptions around healthcare resource use, including differing resource use based on whether a person's condition responds to treatment or not? How valid are the ERG's inclusion and estimation of costs relating to serious adverse events of treatments? Does the frequency of serious adverse events of treatment differ by treatment?

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments Thursday 7 January 2021

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Dr Patricia Keegan**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Jazz Pharmaceutical UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Treatment pathway	
• Is modafinil the standard first line treatment for excessive sleepiness caused by narcolepsy? • Please outline the current treatment pathway for treating excessive sleepiness caused by narcolepsy. • Should additional lines of treatment be modelled (the analysis currently only models 1 line of treatment after modafinil)? • Does the treatment pathway differ for narcolepsy with cataplexy compared to narcolepsy without cataplexy?	Modafinil is the standard and widely used first line therapy for excessive daytime sleepiness due to narcolepsy. This first-line position was established through Key Opinion Leader (KOL) Clinical Practice Interviews, where in answer to the question "What is your first line of treatment for narcolepsy?", all KOLs (n=7, from distinct clinical centres), replied that most or all patients would start on modafinil. This is consistent with the Professional Organisation Submissions for ID1602, in which the Association of British Neurologists (ABN) state that modafinil is first line therapy. Modafinil as first line therapy is also reflected in examples of local treatment pathways (e.g. University Hospital Aintree Sleep Service Pathway, South East London Area Prescribing Committee Pathway for narcolepsy) (1-3). Beyond first line therapy, there is considerable variation in reported pharmacotherapy sequences in the KOL Clinical Practice Interviews and in these local treatment pathways. Both immediate-release (IR) (which is not licensed for use in narcolepsy) and modified-release (MR) (not licensed for use in narcolepsy) formulations of methylphenidate are positioned as second line therapies by both the KOL interviews and the above mentioned pathways. This is consistent with the ABN submission for this Technology Appraisal where they state "amphetamine derived stimulants (dexamphetamine or methylphenidate)" as second line therapy. However, in contrast to this, pitolisant was positioned as a second-line therapy, and sodium oxybate was positioned as a second, third, fourth, and "*last*" line therapy by clinicians in the KOL Clinical Practice Interviews, whereas the ABN submission positions both pitolisant or sodium oxybate as third-line therapy. This variation between the ABN and KOLs is mirrored in the three local treatment pathways mentioned above, and this widespread variability introduces uncertainty about the sequence in which post-modafinil treatments are used in clinical practice. With modafinil firmly established in first line position, Jazz Pharmaceuticals originally considered constructing a treatment-sequence model to reflect this variation in post-modafinil pathways. However, given the variation and inconsistency in the treatment sequences used in practice, and the extreme shortage and unsuitable nature of the clinical efficacy data for some of these treatments (as determined through two systematic literature reviews [SLRs]), an approach to model additional lines of treatment was not feasible. Therefore based on the available efficacy data, Jazz chose an alternative approach that was appropriate to model this evidence. The primary symptom of narcolepsy is excessive daytime sleepiness (EDS). EDS has the largest impact on quality of life in patients with narcolepsy (4-6). The KOL Clinical Practice Interviews indicated that primarily, the treatment strategy is to target

	pharmacotherapy to improving EDS and wakefulness, with the possible addition of an anti-cataplexy medication (from a range potential therapies including tricyclic or SSRI anti-depressants, or sodium oxybate). Therefore, based on the KOL interviews and the few local treatment pathways identified, the focus of treatment in narcolepsy is on managing EDS, and the presence of cataplexy does not impact first or subsequent line treatments for this EDS (1-3).
• Where in the treatment pathway is solriamfetol likely to be used? What factors influence this decision?	Solriamfetol is likely to be used as second-line therapy for EDS associated with narcolepsy. This is influenced by efficacy evidence**,** quality, safety, posology and the license status of current alternatives. Efficacy – there is a paucity of evidence for dexamfetamine and methylphenidate (7), and no randomised-controlled trials were identified in an SLR (for the purposes of the indirect treatment comparison [ITC]). In a subsequent expanded search, only four uncontrolled observational studies were identified, none of which had data that could be incorporated into the ITC. In the General Medical Council document "Good Medical Practice", it is stated that in providing clinical care a doctor must "*provide effective treatments based on the best available evidence*". In this regard, and given the lack of available randomised-controlled evidence, solriamfetol is positioned ahead of both dexamfetamine and methylphenidate. Safety - Many stimulant drugs used for the treatment of narcolepsy, including dexamfetamine, and methylphenidate (unlicensed in narcolepsy) are well known for their addictive profile (8). Further, methylphenidate, dexamfetamine and sodium oxybate are Schedule 2 drugs (9-11). Solriamfetol has been thoroughly tested for its abuse potential; preclinical data, combined with the results of a human abuse potential study (Study 14-001, in which solriamfetol was compared to placebo and the amphetamine stimulant phentermine (12)), indicated that solriamfetol has low potential for abuse, therefore solriamfetol would be preferred in this regard. Posology – Solriamfetol is a once-daily formulation, taken with or without food, and is expected to be less disruptive and more convenient for the patient's daily routine than its comparators. Both IR and MR formulations of methylphenidate (unlicensed in narcolepsy) are available, however even using MR tablets, patients may need to split their dose across the day to maintain wakefulness (13). This is also the case for some patients taking modafinil and dexamfetamine, who may find that the treatment effects wear off in the afternoon and the patient requires an additional dose to boost wakefulness (14, 15). Sodium oxybate is taken at night in two divided doses: the first dose should be taken at bedtime and the second dose should be taken 2.5–4 hours after the first dose (16), which requires the patient to wake up mid-sleep to take their second dose. The only other treatment for narcolepsy with once daily dosing is pitolisant (17). However pitolisant must be taken with food at breakfast (17), which may be unsuitable for patients taking any other medications with breakfast. Pitolisant may induce an increase of stomach acidity (17), which may subsequently be treated using a proton pump inhibitor (PPI) or a histamine-2 receptor blocker (H2RB) thus it may not be suitable for all patients. Furthermore, per its titration schedule, only the 4.5 and 18 mg doses of pitolisant can be achieved with a single tablet (17), and a higher number of pills is reported to impact compliance rates (18) which may both

	impact compliance for patients requiring a greater number tablets to achieve other doses of pitolisant, and represent a 'pill burden' for these patients. License status – Methylphenidate is unlicensed in narcolepsy. Only the IR formulation of dexamfetamine is licensed for use in narcolepsy in the UK. The MHRA state that an unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need. This positions solriamfetol ahead of methylphenidate and some formulations of dexamfetamine with respect to principles of prescribing practice. In contrast, solriamfetol is a licensed treatment that provides sustained wakefulness throughout the day with a once daily dose.
• Is prior modafinil a likely treatment effect modifier for treatments given after modafinil (if yes, is this effect the same for all treatments given after modafinil)? Are other prior treatments likely to be treatment effect modifiers?	Modafinil is not likely to be a treatment effect modifier for subsequent therapies. We could find no evidence of a disease-modifying effect of modafinil in the literature, and patients enrolled in the TONES studies with prior exposure use of narcolepsy medications (including modafinil), demonstrated a return to a baseline ESS level prior to enrolment. Solriamfetol is effective in treating EDS associated with narcolepsy with or without cataplexy (19) as indicated in TONES 2 by its similar effects on Maintenance of wakefulness test (MWT), Epworth sleepiness scale (ESS) and Patient global impression of change (PGI-C) scores, regardless of cataplexy status. It is currently unclear whether cataplexy is an effect modifier for measuring the efficacy of wake-promoting agents. Solriamfetol is not thought to affect cataplexy; pitolisant and sodium oxybate may be used for cataplexy treatment (16, 17, 20). Given the uncertainties around the effect of cataplexy on narcolepsy disease severity and comparisons of drugs that promote wakefulness and treat cataplexy, it was not possible to perform a scenario analysis to examine the effect of cataplexy on EDS response to treatment in the ITC. There are no known treatment effect modifiers with respect to concomitant medications. Solriamfetol is not a substrate or inhibitor of any of the major CYP enzymes, with the exception of weak inhibition of CYP2D6, and is not an inhibitor of renal transporters, with the exception of weak inhibition of OCT2 and MATE1. As such, clinically relevant pharmacokinetic drug interactions are unlikely to occur in patients receiving solriamfetol.
• Are there other factors which are likely treatment effect modifiers (such as cataplexy and containment medications) and what impact could these have on results?	Please refer to the additional response provided below this table, Section 1.1. With respect to solriamfetol comparator treatments, the licences for sodium oxybate, pitolisant and methylphenidate include warnings against the use of alcohol in conjunction with treatment. Methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants and some antidepressants such that when starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times). Dexamfetamine is impacted by a variety of medications that either act to increase or decrease the blood levels of dexamfetamine; conversely dexamfetamine may also increase or decrease the effects of a range of medications. Both methylphenidate and dexamfetamine are contraindicated in patients receiving monoamine oxidase inhibitor treatments. Pitolisant induces CYP3A4

	and CYP2B6 at therapeutic concentrations and its use should therefore be avoided with substrates of CYP3A4 with a narrow therapeutic margin. Conversely, pitolisant metabolism is impacted by potent CYP3A4 inducers and CYP2D6 inhibitors such that dose adjustments may be required; further, antidepressants or antihistamines may impair the efficacy of pitolisant. The use of hormonal contraception may be reduced with pitolisant therefore an alternative method should be used during and for 21 days after treatment discontinuation (17).
• The company should provide alternative scenarios for comparisons of solriamfetol with third and fourth line treatments.	Please refer to the additional response provided below this table, Section 1.1
• The company should provide a scenario in which further lines of treatment are modelled after solriamfetol and the comparator treatments at second-line.	Please refer to the additional response provided below this table, Section 1.1
Issue 2: Comparators	
• How often are dexamfetamine and methylphenidate used after modafinil in clinical practice? How effective are these treatments for treating excessive daytime sleepiness caused by narcolepsy? Should these treatments be	KOL Clinical Practice Interviews indicated that between 20% and 30% of patients on pharmacotherapy are on combinations of medications and the preference is for monotherapy where possible. This is generally consistent with a single centre UK retrospective analysis of patients with narcolepsy (n=116 patients) (21), in which 58.6% (n=68) of patients were taking one wakefulness-promoting agent (WPA), 39.7% were taking 2–3 WPAs and the remaining 2 patients (1.7%) were taking four WPAs. The proportion of patients receiving each medication was: modafinil 54.3%, methylphenidate MR 30.2% (not licensed in narcolepsy), methylphenidate IR 12.9% (not licensed in narcolepsy), dexamfetamine 23.3% and sodium oxybate 36.2% across monotherapy and combination therapy. This is consistent with the expectation that the majority of patients will continue their

included in base case analysis rather than scenario analysis?	first-line modafinil, however the cohort included patients whose EDS was defined as ESS >12, and thus represents a more sleepy population of patients than TONES 2 (ESS ≥10). Mean ESS was not reported in the study however due to the higher inclusion criteria of ESS >12 (compared with the commonly used threshold of ESS >10 in UK practice), the high proportion of patients with refractory sleepiness (39.8%, defined as EDS despite trialling ≥ 3 WPAs) and its similarity to the proportion of patients using combination therapy (~40%), suggests that the proportions of patients receiving each treatment in this single centre study is likely higher than would be expected for the UK average. This is supported by the market share data for treatments outlined in the company submission (CS) which shows the average UK market share (in 2019) for each of these treatments is lower than that observed in this single centre study (21). As outlined in the above responses, and in the additional evidence below this table in Section 1.1, an SLR did not identify any appropriate evidence to allow the inclusion of methylphenidate and dexamfetamine in the ITC. However, using the available evidence identified and assessed as being appropriate to include in the ITC from the clinical trials for the other comparators (sodium oxybate and pitolisant), the analysis showed that the efficacy of solriamfetol and these two comparators is broadly comparable in effect on ESS and MWT. Due to the extreme shortage and unsuitable nature of the efficacy data for dexamfetamine and methylphenidate, it was not possible to consider these in the base case, and the company instead conducted scenario analyses for these comparators.
• What factors influence the choice of treatments used (for example, does the presence of cataplexy impact treatment choices?).	According to the limited number of treatment algorithms available for the management of narcolepsy, the first and subsequent line therapies for the *treatment of EDS* appear to be consistent, and presence of cataplexy as an additional symptom is considered separately with additional/combination treatments (1-3). Treatment of cataplexy as a distinct symptom is most commonly achieved with selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressants (TCA) medications (3, 22). The use of these medications in this way is unlicensed. However, tri or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine) may impair the efficacy of pitolisant because they display histamine H1-receptor antagonist activity and possibly cancel the effect of endogenous histamine released in brain by the treatment (17), thus pitolisant may not be suitable for those using TCAs. It is important to note that KOL feedback indicates that the choice of treatments for the symptoms of narcolepsy is tailored to each individual patient, according to the presence of a given symptom and its impact on function or quality of life. For example, although only licensed in narcolepsy with cataplexy, KOLs advised that sodium oxybate is used in patients with or without cataplexy, depending on clinical need, and some patients receiving sodium oxybate may also be receiving combination therapy.

Issue 3: Generalisability of the clinical trial evidence	
• How generalisable are the results from the TONES trials (particularly TONES 2) to the population seen in clinical practice?	Information on the demographics of the narcolepsy population in the UK is extremely limited. The available data are based on results from three UK Narcolepsy Association surveys[1] which indicate that (23-25): • 51.1–60.7% of patients are female • Median age is 54–56 years • Mean (standard deviation [SD]) ESS scores are: o 19.6 (3.0) for patients with narcolepsy with cataplexy o 16.9 (4.8) for patients with EDS without cataplexy Specifically related to the TONES 2 trial, 65.3% of the patients were female, mean age was 36.2 (SD 13.2) cataplexy was present in 50.8% and mean baseline ESS was 17.2. The characteristics of the trial populations were broadly consistent with those of the UK survey respondents. Approximately 50–60% of the survey respondents were female, compared with approximately two-thirds of the clinical trial populations. The median age of patients in the UK surveys is higher than that observed in the clinical trials, however the dates that the surveys were conducted range from 1998–2004 (thus a new survey may show widely different results – as evidenced by the single centre study described below), and the trials only included adults 18–75 years, whereas the survey patients were 12–89 years old. Furthermore, there is a widely recognised delay to diagnosis for patients with narcolepsy in the UK (26), and these factors may have contributed to the higher median age of the survey respondents. Only one survey reported ESS scores (24), and these were consistent with those of the trial population in that both populations had mean ESS scores outside the normal range (i.e. had ESS scores >10;).

[1] Parkes 1997: 183 patients with narcolepsy, 62 patients with hypersomnia, 10 patients with Obtsructive sleep apnoea and 188 controls returned self-report questionnaires; Daniels 2001: 313/500 patients with narcolepsy returned questionnaires; Morrish 2004: 313/500 patients with narcolepsy returned questionnaires.

	A recent (2020) single centre study of 116 patients with narcolepsy in the UK reported baseline demographics that are also broadly similar to that in TONES 2 (21): • 54.3% were female (vs 65.3% in TONES 2) • Mean age was 39.4 ±14 (vs 36.2±13.2 in TONES 2) • Cataplexy was persistent in 47.3% of narcolepsy type 1 patients (vs a presence of cataplexy in 50.8% of the overall TONES 2 population).
Issue 4: Indirect treatment comparison	
• How robust is the indirect treatment comparison (NMA analysis)? • How uncertain are the comparisons between solriamfetol and the comparator treatments? • Do the results of the indirect treatment comparison, which estimates similar treatment effects (ESS score reduction), for solriamfetol, pitolisant and sodium oxybate, show face validity?	The ITC presented by the company, and the Evidence Review Group's (ERG) modified version of this ITC, both result in solriamfetol being a cost effective treatment option for managing EDS due to narcolepsy. Furthermore, in the event of any uncertainty associated with the ITC, the threshold analyses presented in CS Tables 55 and 56 showed that there were no plausible values that would result in a negative net monetary benefit (NMB) for solriamfetol vs pitolisant nor sodium oxybate.
• Do the ERG additions to the NMA make the indirect treatment analysis more robust? Is a random-effects model or	Jazz is comfortable with the use of either model being used. The ERG additions and random effects model have now been incorporated in an updated version the model that was used as the basis for any analysis in this response document. Whether the random effects or fixed effects model is used has limited impact on the results, with solriamfetol being a cost effective treatment option.

fixed effect model more appropriate to use?	
Issue 5: Subgroup analysis	
• How robust is the subgroup analysis of people who have had previous modafinil? Is this analysis more appropriate to use to inform the cost-effectiveness estimates? • Would a subgroup analysis for people with and without cataplexy be appropriate? Do some of the treatments available treat cataplexy symptoms also?	The results from the prior modafinil sub-group analysis are consistent with the base case analysis, however it is important to note that TONES 2 was not powered to assess any differences in efficacy in patients with and without prior modafinil. It should further be caveated that the ITC was not able to assess subgroups that have previously been treated with modafinil from comparator trials. Notwithstanding this, the threshold analyses presented in the CS show that under all plausible scenarios, solriamfetol is a cost effective treatment option. The company has conducted a new subgroup analysis for patients with/without cataplexy (presented in Table 1 and Table 2, respectively). This analysis shows that in these subgroups solriamfetol remains a cost effective treatment option compared with both sodium oxybate and pitolisant. Cataplexy varies in intensity between patients, ranging from a just-perceptible weakening of the face muscles to more serious episodes such as total collapse onto the floor (27), and Dodel (2007) reported that with the exception of EDS, the symptoms of narcolepsy (including cataplexy) had only a minor impact on patient quality of life (28). This is consistent with the primary focus in UK clinical practice on reduction of EDS (1-3, 22). As mentioned above, for many patients, cataplexy is managed with generic anti-depressants including SSRIs or TCAs. Neither methylphenidate nor dexamfetamine are specifically indicated for cataplexy. Sodium oxybate and pitolisant refer to cataplexy in their indications. However, given the focus in practice on the specific reduction of EDS, the broadly comparable efficacy between solriamfetol, sodium oxybate and pitolisant in reducing ESS described by the ITC, and the results of the new cataplexy subgroup analysis showing that solriamfetol remains cost-effective regardless of cataplexy status, clinician judgement for each individual patient may be the most appropriate means of deciding between solriamfetol and its comparators.
Issue 6: Estimation of the treatment effect	
• Is the approach of using only ESS changes from baseline appropriate? Are there any other clinical	KOLs advice that a reduction in ESS may be used to assess response to treatment (22). The absolute change in ESS from baseline varied between the treatments and as such the level of response will vary amongst responders. Although response to treatment, defined as a 3-point reduction in ESS from baseline, was simply a criterion for the continuation of treatment, the absolute change from baseline was the true measure of treatment efficacy. This is reflective of previous economic evaluations include TA139.

outcomes which can be used to compare treatment effects?	Categorisation of patients into EDS severity bandings – no EDS (ESS: 0-10), mild EDS (ESS: 11-14), moderate EDS (ESS: 15-18), severe EDS (ESS: 18-24) – as outlined by NICE Clinical Knowledge Summary (29), was considered for health states in the current model, but this approach was deemed to be inappropriate for several reasons. Feedback from the KOL Clinical Practice Interviews suggests that in the UK clinicians rarely categorise patients into mild, moderate or severe EDS, and do not use transitions across categories to assess response to treatment (22). In defining EDS categories using ESS scores, some patients could achieve an ESS response (i.e. ≥3 points reduction in ESS) but may not change health state; for example, a patient that improves from ESS=18 to ESS=15 is a 'responder' to treatment but remains within the moderate EDS category. Conversely, patients with baseline ESS scores close to the boundaries between EDS categories may switch health states, in a modelling context, but achieve an ESS improvement that is smaller than the clinical response criteria; for example, a patient that improves by 1 point from ESS=15 to ESS=14 is considered a 'non-responder' to treatment but has switched from a moderate EDS to a mild EDS category; this may inaccurately imply that a patient who achieved a change of health state had a greater improvement than a patient who achieved a 3 point reduction in ESS. In a modelling context, if EDS categorisation had been used to define health states within the current model, this would have resulted in scenarios where patients were receiving and responding to treatment, but were not changing health state (and therefore not achieving any clinical benefit), as defined by a health state related utility, and this patient scenario would therefore underestimate the actual benefit of treatment in the current model. The ESS is a widely used measure in clinical practice, and although the trials identified in the SLR and included in the ITC also reported MWT (thus provided an alternative outcome to compare the treatments), KOLs advised that this measure if rarely used beyond initial diagnosis in UK clinical practice, therefore it was inappropriate to include in the cost-effectiveness analysis
• What is the most appropriate ESS reduction change threshold to use in the analysis to define a response to treatment (reduction of 2 or more, 3 or more, 4 or more, or another threshold)?	The ESS is a useful tool for clinicians, and it is one element considered by clinicians when assessing the sleepiness of a patient. The ESS reduction threshold may therefore be seen as a proxy for a patient feeling a difference in their symptoms after receiving treatment for narcolepsy. KOL advice suggests an ESS reduction of ≥3 points is used to determine a response (22). However, the range of 2 to 4 points is reported in the literature (30-32). An analysis by Lammers 2019 (32) suggests that a proxy for patients feeling a difference is more likely to be closer to 4 points. Therefore Jazz Pharmaceuticals suggests that the most appropriate level is likely to be either 3 or 4 points, but that this should only be used as a proxy for an economic analysis, and that in clinical practice, this threshold should be brought together with the key that a patient feels a meaningful difference. This analysis therefore focused on identifying patients that had responded or not responded to therapy, by looking at the absolute change in ESS from baseline, irrespective of the baseline ESS score. This was expected to be more reflective of UK clinical practice. For the purposes of the analysis response was defined as a ≥3-point reduction in ESS from baseline, the mid-point of the range cited in the literature with scores of 2 and 4 tested in scenario analysis.

• Is the assumption of a constant treatment effect (maintained reduction in ESS from baseline) for those whose condition responds to treatment appropriate? Is it appropriate to assume the same distribution of response (ESS reduction) across all treatments?	Within the economic analysis, the patients who entered the response state were assumed to have a reduced ESS score, specific to the treatment received. Long-term solriamfetol data from TONES 5 demonstrated that in the first year following initiation, the ESS improvement remained relatively constant in responders. The SLR identified one published economic analysis on the cost effectiveness of treatment for narcolepsy from a UK perspective (Lanting 2014 (33)) and the cost-effectiveness analysis in TA139 (which considered continuous positive airway pressure (CPAP) treatment for obstructive sleep apnoea (OSA), another condition in which EDS is a key debilitating symptom) (34, 35). Both of these assessments assumed a constant effect of treatment over the respective model time horizons. Based on these prior analyses and in the absence of any data available for solriamfetol or the comparators to quantify any waning effect, it was assumed that patients that responded to any treatment remained in that response state, using the same treatment-adjusted ESS for the duration of the analysis, unless they discontinued therapy. A scenario analysis was presented in CS Tables 72 and 73 examining the impact of a skewed difference to ESS reductions across all treatments. This showed that the results were largely consistent with the base case, and solriamfetol remained a cost effective treatment option. Furthermore, threshold analyses presented in CS Tables 55 and 56 show that regardless of the change in ESS difference between the comparators solriamfetol remains a cost effective treatment option.
• Is the 8-week timepoint appropriate to capture reduction in ESS treatment effects in the NMA? Does this timepoint underestimate the likely treatment effect of sodium oxybate? If so, is this underestimation likely to be significant?	The analysis assumed that following initiation of therapy, patients will be assessed for response by a specialist at 8 weeks. This is reflective of the available comparator clinical data which had a maximum duration of 8 weeks. The KOL Clinical Practice Interviews showed wide variability with regards to the time at which follow up visits may occur - ranging from 6 weeks to 6 months; in some cases, this is due to limited capacity rather than clinical preference. However, because solriamfetol demonstrated equivalence or greater efficacy to pitolisant or sodium oxybate through the ITC (CS Form B.2.9.2), extending the time to assessing response would mean that patients receiving comparator treatments would inappropriately remain on therapy for longer and accrue the associated drug costs; thus by considering an 8-week time point this reduced unnecessary spending beyond the 8 week assessment and was therefore a conservative assumption for solriamfetol compared with an extended time to assessment on efficacy. As described above, the 8 week timepoint was the longest time point available to all comparators, and that would make comparisons feasible There is no published evidence for sodium oxybate efficacy beyond 9 weeks that could be used to compare its efficacy with solriamfetol at a later time point therefore the impact of this on the sodium oxybate cost-effectiveness within the present analysis cannot be tested. However given that the threshold analyses presented in CS Table 55 show that there is no plausible scenario in which a negative NMB for solriamfetol would be achieved. Therefore it is anticipated that any difference in the time point of assessment used in the analysis would not change the overall conclusions of the base case analysis - that solriamfetol is a cost effective treatment option.

Issue 7: Dosing split	
• What are the most appropriate assumptions relating to the proportion of people on specific doses of each treatment in the analysis (solriamfetol, pitolisant, sodium oxybate, dexamfetamine and methylphenidate)?	**Solriamfetol** Solriamfetol is available as 75 mg and 150 mg film-coated tablets, and the recommended starting dose is 75 mg once daily, upon awakening. The dosing in TONES 2 was determined by randomisation and in TONES 5 patients were protocol-driven to titrate to the highest tolerated dose, thus these studies do not provide a representative breakdown of how solriamfetol would be anticipated to be administered in practice nor the final dose distribution that would be observed. The company propose that the dose splits in the TONES 5 study are not necessarily reflective of how solriamfetol would be used in clinical practice, because investigators were instructed to titrate subjects to the maximum tolerated dose of solriamfetol to maximise therapeutic efficacy; [Academic in confidence information removed]% of patients with narcolepsy were taking a modal dose of 150 mg and [Academic in confidence information removed]% were on the 75 mg dose (36). At the time of writing the CS, the only available evidence of solriamfetol use in clinical practice was that of the real-world usage in the US, where a 50/50 split of solriamfetol between the 75 mg and 150 mg doses was used. The CS, therefore, provided a base case analysis of 50/50. The CS also provided theoretical scenarios of 70/30 and 30/70 (75 mg/150 mg) to illustrate the impact of the dose-split on the overall cost-effectiveness of solriamfetol. The ERG used a base case of 10/90 with scenarios of 20/80 and 0/100 (75 mg/150 mg), and the ERG Report states "*Based on the clinical advice to the company (KOL), treatment dose would generally be titrated to maximum dose*". However, this does not capture the full variability in the KOL responses with English clinicians expressing difficulty in predicting the dose-split of solriamfetol in clinical practice because they had no prior experience with the product. Only 5 of 7 KOLs described titration and the responses varied according to the specific treatment. • 1 said they would escalate through drug class rather than increase the dose • 1 said they would push to higher doses in refractory patients but clarified that not many patients reach the highest dose of dexamfetamine (60 mg), consistent with another KOL who specified they titrate slowly to 30 mg per day. • 3 KOLs said they would titrate to the maximum dose, however two of these specified that they would titrate 'low and slow' and the third didn't describe the titration process. These descriptions of treatment titration refer to monotherapy, whereas several clinicians reported that they would use combinations of existing therapy options where additional wakefulness is needed. Thus it seems unlikely that 80–100% of patients would be titrated to the solriamfetol 150 mg dose. Furthermore, it is important to acknowledge that in the patients who achieved a 3 point reduction in ESS, those receiving solriamfetol 75 mg improved by ~7.39 points versus 7.51 for solriamfetol

	150 mg, but a larger proportion of patients achieve a 3 point improvement on the higher dose. The de novo National Health and Wellness Survey (NHWS) analysis shows that if a patient has normalised with treatment (achieved ESS ≤10), there is little additional benefit to further reducing ESS. Therefore, keeping patients on the lowest dose that either normalises or achieves a ≥3 point reduction (i.e. response) is a cost effective strategy. The CS was submitted in January 2020 and since then solriamfetol has been available in France and Germany, and has generated real-world data on dose splits in Europe. Solriamfetol has been prescribed in France since April 2020, and as of December 2020, the average dose-split across that 8 month period is [Commercial in confidence information removed] (75 mg/150 mg). Solriamfetol has been prescribed in Germany since May 2020, and as of December 2020, the average dose-split over that 7 month period is [Commercial in confidence information removed] (75 mg/150 mg). Thus the CS base case of 50/50 is the best estimation of the anticipated dose-split for clinical practice in England. **Comparators** The CS did not provide dose-split scenarios for the comparator drugs sodium oxybate and pitolisant. The ERG considered that the dose splits in the company's base case for both sodium oxybate and pitolisant were reasonable: • The base case for pitolisant was derived from NICE Evidence Summary 8, in which the manufacturer (Lincoln Medical Ltd) estimated that approximately one third of patients would be maintained on 18 mg per day and two thirds on 36 mg per day. The base case analyses for pitolisant were restricted to combined dose analyses (≤40mg) due to an absence of effectiveness estimates stratified by dose for pitolisant. • For sodium oxybate, there are no available data on the proportion of patients who would reach the respective final doses for sodium oxybate (4.5, 6, and 9 g). The CS, therefore, presented the doses individually, and also presented a weighted average for all sodium oxybate doses for consideration using an equal dose split across the three formulations. This equates to an average daily dose of 6.5 g thus can be considered a conservative approach to modelling the CE of solriamfetol vs sodium oxybate, compared with using the World Health Organisation (WHO) defined daily dose for sodium oxybate of 7.5 g (37). In addition to the ERG agreeing that the company's base case dose splits for sodium oxybate and pitolisant were reasonable, the ERG also provided further scenario analyses which investigated the impact of varying dose splits of sodium oxybate (10/10/80 and 0/0/100 for 4.5, 6 and 9 g doses), and exploratory analysis to investigate the impact of varying dose splits of pitolisant (between 10 and 30% of patients on the lowest 4.5 g dose). However, none of these results produced an NMB below £0 at a willingness to pay threshold of £20,000 per Quality Adjusted Life Year (QALY) gained. Regardless of the dose splits used for sodium oxybate and pitolisant, solriamfetol was always cost-effective vs the comparators.

	In terms of dose splits for methylphenidate and dexamfetamine, a SLR and an extended SLR were conducted but there was due to the extreme shortage and unsuitable nature of the efficacy data for dexamfetamine and methylphenidate therefore none of the evidence identified allowed methylphenidate or dexamfetamine to be incorporated into the ITC. Based on the above narrative, the additional response information provided in Section 1.1, and the information provided in response to Issue 1, the overall model approach can be considered a conservative approach that makes appropriate use of the available evidence in terms of comparator efficacy, dose splits and time points of assessment to treatment response.
• The technical team considered that clinical advice is needed on: The likely dose split of solriamfetol based on use of the treatment in clinical practice in England, and what factors influence this.	Please refer to the additional response provided below this table, Section 1.2
• How frequently do people change doses or treatments? What factors influence this?	The KOL Clinical Practice Interviews highlighted that the treatment approach for narcolepsy is based on clinical judgement and patients' subjective reports of their symptoms. Patients with narcolepsy tend to be managed on an individual basis, with treatment adjusted in accordance with individual patient response and the impact of their symptom on daily function. Patients can, and do, have their dose adjusted to balance optimal treatment effectiveness and the risk of side effects. The KOL Clinical Practice Interviews showed that factors that influence changing doses or treatment include lack of efficacy, side effects, tolerability, and patient choice. As such, the frequency at which patients change dose or treatments, and the factors that determine any changes, are likely to vary widely across sleep centres, patients and regions.
Issue 8: Treatment discontinuation	
• Are the simplifying assumptions in the model appropriate, including the assumptions that treatment discontinuation rates (resulting from a lack of response or	Scenario analyses show that for a range of discontinuation rates tested between comparators (either constant or differential), solriamfetol remains a cost effective treatment option. The application of treatment differences from the ITC to the TONES 2 patient level data may be considered a simplification, however the credible intervals from the ITC overlap which would merit using a cost minimisation analysis in some

treatment emergent adverse events) are the same for all treatments and that ESS score reductions are constant for people whose disease responses to treatments?	circumstances, and due to the low cost of solriamfetol in using a cost minimisation methodology, solriamfetol would remain a cost effective treatment option (compared with pitolisant and sodium oxybate).
• NICE requested that the company provide a scenario analysis based on the results from the ITC for discontinuation resulting from serious TEAEs (as suggested by the ERG).	Please refer to the additional response provided below this table, Section 1.3
• NICE requested that the company provide a scenario analysis that applies a different rate of treatment discontinuation over the longer term to demonstrate the impact of this on results.	Please refer to the additional response provided below this table, Section 1.3
Issue 9: Resource use	
• How appropriate is the ERG's assumptions around healthcare resource use, including differing resource use based on whether a person's condition responds to treatment or not?	The ERG have assumed that serious adverse events are dose dependent, based in isolation on information from the TONES 5 trial, in which there were n=3 serious adverse events in the narcolepsy population and in the licensed doses of 75 and 150 mg. This assumption by the ERG does not appear to consider that patients were protocol-driven to titrate to the highest tolerated dose and that the 75 mg and 150 mg groups in TONES 5 were not numerically balanced (n=15 and n=63 patients with narcolepsy respectively). As no serious adverse events occurred in the 75 mg arm (creating a zero numerator), it would be reasonable to consider that a single serious adverse event in this arm would render the populations balanced, undermining this assumption. This has not

• How valid are the ERG's inclusion and estimation of costs relating to serious adverse events of treatments? Does the frequency of serious adverse events of treatment differ by treatment?	been considered in a sensitivity analysis by the ERG. In contrast, in TONES 2, serious adverse events occurred in 0, 0, and 1 patient for placebo, solriamfetol 75 mg and 150 mg doses, respectively. We agree with the ERG's assessment that the absolute incidence of serious adverse events is low for solriamfetol. We are also pleased that the approach to consider that most adverse events occur early in the course of treatment, are self-limiting and resolve quickly, was considered reasonable by the ERG. The estimation of costs relating to serious adverse events is based on hospitalisations due to sleep disorders, rather than the presenting complaint: the adverse event. Given that the nature of the admissions that informed the estimated mean admission duration of 3.5 days in Germany (28), the applicability of this to the UK healthcare environment is unclear. This cohort, on which the duration of admission is based, included accidents directly related to narcolepsy, data which was not reported in the TONES 2 or 5 study groups. This biases the estimate towards longer admissions, with more severe affected patients (as acknowledged by the ERG) which limits the reliability of this estimate. The anticipated frequency of serious adverse events does differ by treatment. For example, for both methylphenidate and dexamfetamine, arrhythmias are "common or very common" (10, 11) whereas tachycardia is "uncommon" for solriamfetol (20). In a UK retrospective case-series of narcolepsy (and idiopathic hypersomnia) patients treated with modafinil, stimulant therapy, and sodium oxybate, significant side-effects were common (38). This is in contrast to the TONES 5 study, where solriamfetol TEAEs were mild or moderate in severity (39).

1. Additional responses to the TE questions

1.1 Issue 1: Treatment pathway – Additional Response

Scenario Analyses Response

- **The company** should provide alternative scenarios for comparisons of solriamfetol with third- and fourth- line treatments.
- **The company** should provide a scenario in which further lines of treatment are modelled after solriamfetol and the comparator treatments at second line

As described in the CS, modafinil is widely established as the first-line treatment of choice, whereas there is no established pathway for patients with narcolepsy in whom modafinil has failed, is not tolerated or is contraindicated. The CS outlines the extensive searches taken to identify any evidence for comparators – a systematic literature review for randomised controlled trials (RCTs), followed by an additional search for studies of any study design, were carried out but neither search identified evidence of a suitable quality to allow methylphenidate or dexamfetamine to be incorporated into the ITC (either from RCTs or from observational studies). This lack of clinical effectiveness evidence was acknowledged by the ERG. Therefore, the analysis originally provided by the company considers all comparators for which robust clinical evidence was available, i.e. pitolisant and sodium oxybate.

If dexamfetamine or methylphenidate are considered second/third line treatments, then the comparators at third/forth line would be pitolisant and sodium oxybate. Therefore, any analysis that would include dexamfetamine or methylphenidate would be aligned with the current comparators in the CS base case. However, due to the lack of clinical data identified for dexamfetamine or methylphenidate, despite extensive searches, the company feels it is not possible, nor would it be appropriate, to include dexamfetamine or methylphenidate within the base case analysis. As such, the appropriate comparators to include in the cost-effectiveness model remain pitolisant and sodium oxybate.

Whilst it is acknowledged that some clinicians, including the submission from the professional group, may consider dexamfetamine and methylphenidate as a second/third line treatment, the Sleep Services Analysis (consisting of 9 respondents) and KOL Clinical Practice Interviews (consisting of 7 clinicians) indicate that this treatment sequence is not established nor consistent across the UK, further supporting the current comparators included in the base line analysis. Further, it is important to note that in some cases, dexamfetamine or methylphenidate may be used as add-on therapies to modafinil, therefore accruing the cost of two treatments simultaneously. Additionally, due to the potential pharmacological tolerance that can be associated with amphetamines and derivatives as a medication classes (40, 41), patients may experience a reduction in efficacy in the long-term, and in order to prolong their efficacy in the longer-term, some patients choose to take a break from dexamfetamine/methylphenidate on some days (e.g. taking a break at the weekends, or during holidays). Modelling against methylphenidate/dexamphetamine may require a different approach containing the below listed features, however these approaches were not possible due to the extreme shortage and unsuitable nature of the efficacy data for dexamfetamine and methylphenidate:

- taking into account an escalating cost and adverse event (AE) profile
- some clinicians described advising treatment breaks for stimulant therapy (“sometimes encouraged to have a break in stimulant treatment in summer or over the weekend”), or know that this is how patients manage their own therapy to avoid side effects of stimulants (“[many patients] on high doses of modafinil and methylphenidate choose to go without treatment for short periods such as on weekends and on holidays mainly to avoid side effects”)

- Some KOLs advise that patients are unable to tolerate methylphenidate and dexamfetamine, and it may not be possible to titrate to a dose that results in a clinically meaningful effect without tolerable side effects.
- KOLs advise that some patients receive stimulants to provide short term boosts in wakefulness, and stimulants are sometimes used as occasional add-on therapy to a patient's primary treatment for EDS. However, due to the potential pharmacological tolerance that can be associated with amphetamines and derivatives as a medication classes (40, 41), if a patient has become tolerant to their treatment effects, the treatment efficacy could be diminished over time. The tolerance that some KOLs may be associated with long term use of methylphenidate and dexamfetamine may therefore necessitate the need to incorporate a 'loss of treatment efficacy' element to a model and an associated reduction in QoL over time.

It is acknowledged that in clinical practice, patients who do not respond to a second line (or subsequent line) of treatment may receive another therapy, however due to the wide variation in the treatment pathway it is unclear what this subsequent treatment may be. With the current modelling approach all patients who do not respond to a therapy are treated in the same way (i.e. they are assumed to return to their baseline levels of ESS with no treatment costs). By applying this assumption to all comparators, and with the assumption that all products considered are discontinued at the same rate, it is felt that the inclusion of subsequent lines of treatment within the model will not change the incremental costs and QALY differences and so the results presented will remain unchanged. As previously described, an SLR was conducted for the comparators but there was extreme shortage of efficacy data for dexamfetamine and methylphenidate; there were also limited numbers of randomised controlled trials identified for sodium oxybate and pitolisant. Although not specifically targeted in the SLR, it can be assumed there is an absence of evidence for the efficacy of the comparators and solriamfetol at different lines of treatment. A treatment sequencing model was considered, but was not possible due to the absence of data; were the data available, not only would this add considerable complexity to a model (for the reasons outlined above), but given that solriamfetol is broadly as effective as the comparators and due to its lower list price, it is likely that this model approach would show that solriamfetol is cost effective.

Clinician advice is that treatment combinations and treatment sequences for patients with narcolepsy are extremely variable in the UK, other than the position of modafinil first-line. Whether patients will respond to treatment, and if so, the level of response to that treatment (in terms of reduction in EDS) can be expected to vary widely due to the individual nature of the impact of EDS. As such, even if robust clinical effectiveness evidence were available for all of the comparators included in the decision problem, it may not be appropriate to model their efficacy at subsequent lines of treatment post-modafinil, in part due to the use of combination therapy, and in part as this may incorrectly imply that there is an established treatment sequence across the UK. Similarly, this may incorrectly imply that any one sequence would be suitable for this cohort of patients however the wide variability observed in clinical practice in terms of treatment sequences and/or use of combination treatments (as outlined by the KOLs and Sleep Services Analysis) is likely a reflection of the variability required to achieve management of EDS in patients with narcolepsy.

Cataplexy scenario

The technical team considers that clinical advice is needed on: whether cataplexy and the related use of concomitant medication are potential treatment effect modifiers and to what extend this may add to the uncertainty in the indirect treatment comparison.

Within TONES 2, at randomisation approximately 50% of the patients had cataplexy. A scenario analysis of subgroups with/without cataplexy was considered and the results are presented in Table 1 and Table 2, respectively. Limiting the analysis to those patients with or without cataplexy does not alter the conclusion of the base case analysis, and solriamfetol remains a cost-effective treatment compared to both sodium oxybate and pitolisant.

Table 1. Scenario analysis: Presence of cataplexy

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,670	13.241	42.212			
Pitolisant	£19,953	13.252	42.212	£11,283	0.011	£1,028,258
Sodium oxybate	£26,961	13.204	42.212	£7,008	-0.048	Dominated

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

Table 2. Scenario analysis: Absence of cataplexy

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£7,992	13.337	41.719			
Pitolisant	£18,567	13.344	41.719	£10,575	0.007	£1,479,712
Sodium oxybate	£24,818	13.307	41.719	£6,251	-0.037	Dominated

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

1.2 Issue 7: Dose split – Additional Response

The technical team considered that clinical advice is needed on: The likely dose split of solriamfetol based on use of the treatment in clinical practice in England, and what factors influence this.

Based on the report received: "ID1602 solriamfetol tech report v0.18 to PM for technical engagement [AiC]", the base case model has been modified to reflect the comments from technical team report with regards to:

- **Indirect treatment comparison (ITC):** The technical team accepts that the degree of heterogeneity does not prevent the use of an network meta-analysis (NMA) in this appraisal and considers that the analysis based on the **random effects** model are likely to be more appropriate. The technical team also agree with the ERG's inclusion of the **Harmony Ibis and modafinil data from Harmony Ibis and the Dauvilliers (2013) trials**.
    - The model has therefore been updated using a revised ITC which includes these studies and based the analysis on the random effects model.
- **Dosing splits:** The technical team consider that the most appropriate dosing split assumptions for solriamfetol are likely to be closer to the ERG assumptions (that is, a higher proportion of people would be given the 150 mg compared to the 75 mg dose).
    - Since the original submission solriamfetol has now been launched in Europe and preliminary prescribing data is now available for France and Germany.
    - In France, the current prescribing split in narcolepsy patients is [Commercial in confidence information removed] at 75 mg and [Commercial in confidence information removed] at 150 mg
        - This data has been used in the revised base case.
    - In Germany, the current prescribing split in narcolepsy patients is [Commercial in confidence information removed] at 75 mg and [Commercial in confidence information removed] at 150 mg.
        - A scenario using this data is also considered.

It is noted that the technical team agreed with the ERG that combined-dose analysis is appropriate as it more closely reflects the use of these treatments in NHS clinical practice. The results are therefore presented in this format.

Scenario analysis: French prescribing data

The original company base case is presented in Table 3. For comparative purposes, across the requested scenarios a revised base case using the updated ITC and dosing split based on real world prescribing data from France is presented in Table 4.

The revised ITC results lead to small increases in total QALYs across all treatments but the impact on pitolisant was smaller than that observed for solriamfetol and sodium oxybate, this leads to a reduced QALY gain for pitolisant over solriamfetol compared with the original base case. Consequently, the incremental cost effectiveness ratio (ICER) versus pitolisant has increased (in the South-West quadrant) and improves the cost-effectiveness of solriamfetol; solriamfetol continues to dominate sodium oxybate. Overall, the conclusions remain unchanged vs the CS base case analysis. This result is easy to interpret, but it is important to acknowledge that as outlined in the response to Issue 7 above, many patients who respond to the 75 mg dose will not need to titrate to the highest dose as there is no additional benefit to their ESS score at the 150 vs 75 mg dose.

Table 3. Original 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

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

Table 4. Revised company base case results for combined doses

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,322	13.368	42.445			
Pitolisant	£19,242	13.376	42.445	£10,920	0.008	£1,352,843
Sodium oxybate	£25,860	13.336	42.445	£6,618	-0.040	Dominated

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

Scenario analysis: German prescribing data

As noted above, new European prescribing data is now available and the French data is used in the revised base case (Table 4). The German prescribing data is slightly different and so for completeness a scenario analysis is presented in Table 5.

Table 5. Scenario: German prescribing split ([Commercial in confidence information removed] at 75 mg and [Commercial in confidence information removed] at 150 mg)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£7,891	13.362	42.445			
Pitolisant	£19,242	13.376	42.445	£11,352	0.014	£800,806
Sodium oxybate	£25,860	13.336	42.445	£6,618	-0.040	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

As with the revised base case data, incorporating the German prescribing data does not change the overall conclusions of the analysis with solriamfetol remaining the cost-effective treatment of choice.

1.3 Issue 8: Treatment discontinuation – Additional Response

The company should provide a scenario analysis based on the results from the ITC for discontinuation resulting from [serious] TEAEs (as suggested by the ERG).

Note: there was no ITC analysis performed for "Discontinuation resulting from *serious* treatment-emergent adverse events (TEAEs)" neither by the company nor the ERG – this appears to be a typographical error, therefore "Discontinuation resulting from *any* TEAE" is presented here.

Updated discontinuation analysis

We are pleased to note that the ERG considered the company's assumptions relating to treatment discontinuation resulting from adverse events to be reasonable, acknowledging that the rate may be overestimated because of TONES 5 inclusion of the unlicensed 300 mg solriamfetol dose. As noted, the ITC does provide an alternative potential data source and for the purposes of this scenario the updated ITC (including the Harmony Ibis and the Dauvilliers (2013) trials) has been used (Table 6).

Table 6. Discontinuation due to TEAEs 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, odds ratio								
Placebo	41.97	4.004	1303	(0.421, 120.8)	61280	4.318	1E+07	(0.006, 3962)
Solriamfetol 75 mg	40.79	4.015	2181	(0.415, 122)	37420	4.208	4E+06	(0.006, 3941)
Pitolisant ≤ 40 mg	124.4	7.292	4266	(0.348, 370.7)	3E+06	7.021	8E+08	(0.002, 28900)
Sodium Oxybate 4.5 g	490.9	4.859	39440	(0.062, 631.4)	8E+07	5.182	2E+10	(0, 82970)
Sodium Oxybate 6 g	15.62	0.741	775.1	(0.013, 40.29)	5E+06	0.756	1E+09	(0, 9281)
Sodium Oxybate 9 g	10.29	0.685	300.1	(0.012, 38.04)	2E+07	0.677	6E+09	(0, 7910)
Absolute treatment effects, proportion of patients discontinuing due to TEAEs								
Placebo	0.015	0.014	0.008	(0.004, 0.033)	0.014	0.012	0.007	(0.003, 0.031)
Solriamfetol 75 mg	0.039	0.014	0.078	(0, 0.245)	0.107	0.013	0.221	(0, 0.911)
Solriamfetol 150 mg	0.099	0.054	0.127	(0.006, 0.488)	0.187	0.052	0.276	(0, 0.974)
Pitolisant ≤ 40 mg	0.012	0.008	0.014	(0.001, 0.048)	0.047	0.008	0.126	(0, 0.466)
Sodium Oxybate 4.5 g	0.035	0.012	0.07	(0, 0.223)	0.098	0.011	0.213	(0, 0.896)
Sodium Oxybate 6 g	0.121	0.071	0.139	(0.009, 0.551)	0.206	0.067	0.285	(0, 0.98)
Sodium Oxybate 9 g	0.13	0.077	0.151	(0.01, 0.602)	0.217	0.075	0.291	(0, 0.982)

Abbreviations: CrI, credible interval; SD, standard deviation; TEAE, treatment-emergent adverse event.

In the CS base case analysis, using data from TONES 5, it was assumed that 10.2% of patients on solriamfetol would discontinue due to TEAEs but that most of these discontinuations (56.8%) will occur within the first 4 weeks of treatment and are therefore already reflected in the initial phase of the model which is based on the IPD data. Adjusting for this early discontinuation results in an annual rate of discontinuation due to AEs of 4.4% for solriamfetol. This rate was applied to all comparators because the ITC did not demonstrate a statistically significant difference in the rates of discontinuation due to TEAEs between comparators. The ITC results have therefore been be adjusted to reflect the early discontinuations due to TEAEs with the assumption that 56.8% of these discontinuations will also occur in the first 4 weeks (Table 7).

Table 7. Adjusted absolute proportion of patients discontinuing due to TEAEs from ITC

	Fixed effect		Random effects	
	Mean from ITC	Adjustment for 1st 4-weeks	Mean from ITC	Adjustment for 1st 4-weeks
Solriamfetol 75 mg	3.9%	1.7%	10.7%	4.6%
Solriamfetol 150 mg	9.9%	4.3%	18.7%	8.1%
Pitolisant ≤ 40 mg	12.0%	5.2%	4.7%	2.0%
Sodium Oxybate 4.5 g	3.5%	1.5%	9.8%	4.2%
Sodium Oxybate 6 g	12.1%	5.2%	20.6%	8.9%
Sodium Oxybate 9 g	13.0%	5.6%	21.7%	9.4%

Abbreviations: ITC, indirect treatment comparison

Fixed vs random effects

Due to the high degree of uncertainty with the ITC, the results between the fixed and random effects model vary significantly therefore scenario analysis considering both are presented in Table 8 and Table 9, respectively.

When the proportion of patients discontinuing due to TEAEs from the fixed effects model are used both pitolisant and sodium oxybate are dominated (i.e. more costly and less effective) by solriamfetol (Table 8).

Table 8. Proportion of patients discontinuing due to TEAEs from ITC (Fixed effects)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,842	13.386	42.445			
Pitolisant	£18,490	13.366	42.445	£9,648	-0.020	Dominated
Sodium oxybate	£25,326	13.335	42.445	£6,837	-0.031	Dominated

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

When the proportion of patients discontinuing due to TEAEs from the random effects model are used pitolisant is still dominated by solriamfetol, however sodium oxybate moves onto the cost-effectiveness frontier (Table 9). However, the incremental cost between solriamfetol and sodium oxybate is £14,452 and the incremental QALY gain is 0.066, resulting in an incremental cost-effectiveness ratio of £217,915 per QALY indicating that sodium oxybate would not be considered cost-effective with the traditional cost-effectiveness thresholds, therefore leaving solriamfetol as the cost-effective treatment.

Table 9. Proportion of patients discontinuing due to TEAEs from ITC (Random effects)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£7,429	13.345	42.445			
Pitolisant	£21,404	13.303	42.445	£13,975	-0.042	Dominated
Sodium oxybate	£21,881	13.411	42.445	£477	0.108	£4,415

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

The results of this scenario analysis demonstrate that considering the results from the ITC for discontinuation resulting from TEAEs does not change the overall conclusion of the base case analysis but do highlight the significant uncertainty associated with the ITC.

Alternative discontinuation rates in the long term

- The company should also provide a scenario which applies a different rate of treatment discontinuation over the longer term to demonstrate the impact of this on results. Clinician input is needed on how treatment discontinuation rates may change over the longer term.

In the original CS, a range of scenarios considering different discontinuation rates due to both loss of response and due to TEAEs were presented. The following hypothetical scenarios where considered:

- Discontinuation rates for the comparators, from year two onwards, are set to half the current value
- Discontinuation rates for the comparators, from year two onwards, are set to zero
- Discontinuation rates for the comparators, from year two onwards, are set to twice the current value

Each of these scenarios has been amended to reflect the revised base case:

Table 10. Discontinuation rates for the comparators, from year two onwards, are set to half the current value

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,322	13.368	42.445			
Pitolisant	£29,942	13.517	42.445	£21,620	0.149	£145,063
Sodium oxybate	£40,305	13.454	42.445	£10,363	-0.063	Dominated

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

Table 11. Discontinuation rates for the comparators, from year two onwards, are set to zero

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,322	13.368	42.445			
Pitolisant	£68,712	14.028	42.445	£60,390	0.660	£91,523
Sodium oxybate	£92,646	13.882	42.445	£23,935	-0.145	Dominated

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

Table 12. Discontinuation rates for the comparators, from year two onwards, are set to twice the current value

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,322	13.368	42.445			
Pitolisant	£11,955	13.280	42.445	£3,633	-0.088	Dominated
Sodium oxybate	£16,022	13.255	42.445	£4,067	-0.025	Dominated

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

As observed in the CS cost-effectiveness analysis, in these updated conservative scenarios with reduced discontinuation for pitolisant and sodium oxybate, the costs for each treatment increase as a result of more patients remaining on treatment and the QALYs also increase accordingly. However, these changes still result in solriamfetol dominating sodium oxybate, and the ICER for pitolisant exceeding traditionally accepted thresholds. In the alternative scenario where discontinuation increases with the comparators, solriamfetol dominates both pitolisant and sodium oxybate.

Similar hypothetical scenarios in which discontinuation rates are halved or doubled for solriamfetol but the comparators remain unchanged, result in very similar results (Table 13 and Table 14). In all scenarios, solriamfetol remains cost-effective versus both pitolisant and sodium oxybate.

Table 13. Discontinuation rates for the solriamfetol, from year two onwards, are set to half the current value

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£12,973	13.505	42.445			
Pitolisant	£19,242	13.376	42.445	£6,269	-0.128	Dominated
Sodium oxybate	£25,860	13.336	42.445	£6,618	-0.040	Dominated

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

Table 14. Discontinuation rates for the solriamfetol, from year two onwards, are set to twice the current value

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£5,154	13.275	42.445			
Pitolisant	£19,242	13.376	42.445	£14,088	0.101	£139,475
Sodium oxybate	£25,860	13.336	42.445	£6,618	-0.040	Dominated

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

References

1. South East London Area Prescribing Committee. Pathway for the pharmacological management of excessive daytime sleepiness due to narcolepsy. 2018. Available from: http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Clinical%20guidelines%20and%20pathways/SLEEP%20Narcolepsy%20pathway%20Aug%202018.pdf. Accessed on: 6th January 2021
2. Northern Treatment Advisory Group. Pitolisant for Narcolepsy Treatment Pathway. 2018. Available from: http://ntag.nhs.uk/docs/NTAG%20Pitolisant%20Pathway%20-%20final.pdf. Accessed on: 6th January 2021
3. Pan Mersey Area Prescribing Committee. Narcolepsy. University Hospital Aintree Sleep Service Pathway. 2019. Available from: https://www.panmerseyapc.nhs.uk/media/2178/narcolepsy.pdf. Accessed on: 6th January 2021
4. Ozaki A, Inoue Y, Hayashida K, Nakajima T, Honda M, Usui A, et al. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naive patients and the general Japanese population. Sleep Med. 2012;13(2):200-206.
5. Vignatelli L, Plazzi G, Peschechera F, Delaj L, D'Alessandro R. A 5-year prospective cohort study on health-related quality of life in patients with narcolepsy. Sleep Med. 2011;12(1):19-23.
6. Ervik S, Abdelnoor M, Heier MS, Ramberg M, Strand G. Health-related quality of life in narcolepsy. Acta neurologica Scandinavica. 2006;114(3):198-204.
7. Billiard M, Dauvilliers Y, Dolenc-Grošelj L, Lammers GJ, Mayer G, Sonka K. Ch 38. Management of Narcolepsy in Adults. In: Gilus N, Barnes M, Brainin M, editors. European Handbook of Neurological Management. 1. 2nd ed. Chichester, West Sussex, United Kingdom: John Wiley & Sons; 2011. p. 513-528.
8. Bisagno V, Gonzalez B, Urbano FJ. Cognitive enhancers versus addictive psychostimulants: The good and bad side of dopamine on prefrontal cortical circuits. Pharmacol Res. 2016;109:108-118.
9. British National Formulary. Sodium Oxybate. 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/sodium-oxybate.html. Accessed on: 6th January 2021
10. British National Formulary. Dexamfetamine sulfate. 2019. Available from: https://bnf.nice.org.uk/drug/dexamfetamine-sulfate.html. Accessed on: 6th January 2021
11. British National Formulary. Methylphenidate Hydrochloride. 2019. Available from: https://bnf.nice.org.uk/drug/methylphenidate-hydrochloride.html. Accessed on: 6th January 2021
12. Carter LP, Henningfield JE, Wang YG, Lu Y, Kelsh D, Vince B, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the human abuse liability of solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor. J Psychopharmacol. 2018;32(12):1351-1361.
13. Guy's and St Thomas' NHS Foundation Trust. Methylphenidate for the treatment of narcolepsy. 2018. Available from:

https://www.guysandstthomas.nhs.uk/resources/patient-information/pharmacy/methylphenidate.pdf. Accessed on: 6th January 2021

14. Harvard Medical School: Division of sleep medicine. Narcolepsy: Medications. 2018. Available from: http://healthysleep.med.harvard.edu/narcolepsy/treating-narcolepsy/medications. Accessed on: 6th January 2021
15. Schwartz JRL, Feldman NT, Bogan RK, Nelson MT, Hughes RJ. Dosing Regimen Effects of Modafinil for Improving Daytime Wakefulness in Patients With Narcolepsy. Clinical Neuropharmacology. 2003;26(5):252-257.
16. UCB Pharma. Sodium oxybate (Xyrem) 500mg/ml summary of product characteristics. 2019. Available from: https://www.medicines.org.uk/emc/product/178. Accessed on: 6th January 2021
17. Lincoln Medical Ltd. Pitolisant (Wakix) summary of product characteristics. 2016. Available from: https://www.medicines.org.uk/emc/product/7402. Accessed on: 6th January 2021
18. Pan F, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adherence to prescription medications. J Gen Intern Med. 2008;23(5):611-614.
19. Dauvilliers Y, Verbraecken J, Partinen M, Hedner J, Saaresranta T, Georgiev O, et al. Pitolisant for Daytime Sleepiness in Obstructive Sleep Apnea Patients Refusing CPAP: A Randomized Trial. Am J Respir Crit Care Med. 2020;201(9):1135-1145.
20. Jazz Pharmaceuticals. Solriamfetol (Sunosi) summary of product characteristics. 2020. Available from: https://www.medicines.org.uk/emc/product/11016/smpc. Accessed on: 6th January 2021
21. Perez-Carbonell L, Lyons E, Gnoni V, Higgins S, Otaiku AI, Leschziner GD, et al. Adherence to wakefulness promoting medication in patients with narcolepsy. Sleep Med. 2020;70:50-54.
22. Jazz Pharmaceuticals. **CONFIDENTIAL.** KOL Clinical Practice Interviews. 2019.
23. Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. Journal of Sleep Research. 2001;10(1):75-81.
24. Parkes J, Chen S, Clift S, Dahlitz M, Dunn G. The clinical diagnosis of the narcoleptic syndrome. Journal of Sleep Research. 1998;7(1):41-52.
25. Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Medicine. 2004;5(1):37-41.
26. Leschziner G. Narcolepsy: a clinical review. Pract Neurol. 2014;14(5):323-331.
27. Narcolepsy UK. Resouces - Cataplexy. 2020. Available from: https://www.narcolepsy.org.uk/resources/cataplexy. Accessed on: 6th January 2021
28. Dodel R, Peter H, Spottke A, Noelker C, Althaus A, Siebert U, et al. Health-related quality of life in patients with narcolepsy. Sleep Medicine. 2007;8(7-8):733-741.
29. National Institute for Health and Care Excellence. Obstructive sleep apnoea syndrome, Clinical Knowledge Summary. 2015. Available from: https://cks.nice.org.uk/obstructive-sleep-apnoea-syndrome#!diagnosisAdditional. Accessed on: 6th January 2021
30. Scrima L, Emsellem HA, Becker PM, Ruoff C, Lankford A, Bream G, et al. Identifying clinically important difference on the Epworth Sleepiness Scale: results from a narcolepsy clinical trial of JZP-110. Sleep Med. 2017;38:108-112.

31. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, et al. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2018;197(7):961-963.

32. Lammers G, Bogan R, Schweitzer PK, Menno D, Carter J, Bron M, et al., editors. Oral Presentation 32: Thresholds for Clinically Meaningful Changes on the Epworth Sleepiness Scale and Maintenance of Wakefulness Test Sleep Latency (Abstract A-1055-0019-00815). World Sleep; 2019 20 - 25 September Vancouver, Canada: Sleep Medicine.

33. Lanting L, Roome C, Lang L, Stein K. Sodium oxybate for narcolepsy with cataplexy - A cost-effective analysis. Journal of Neuroinfectious Diseases. 2014;5:2.

34. McDaid C, Griffin S, Weatherly H, Duree K, Van der Burgt M, Van Hout S, et al. NICE TA139 Assessment report: The Continuous Positive Airway Pressure for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. 2007.

35. National Institute for Health and Care Excellence. TA139 Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome 2008. Available from: https://www.nice.org.uk/guidance/ta139/resources/continuous-positive-airway-pressure-for-the-treatment-of-obstructive-sleep-apnoeahypopnoea-syndrome-pdf-82598202209221. Accessed on: 6th January 2021

36. Jazz Pharmaceuticals. **CONFIDENTIAL**. TONES 5 Clinical study report. A long-term safety and maintenance of efficacy study of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy or obstructive sleep apnoea. 2018.

37. World Health Organisation. Sodium Oxybate Defined Daily Dose. 2019. Available from: https://www.whocc.no/atc_ddd_index/?code=N07XX04&showdescription=yes. Accessed on: 6th January 2021

38. Thakrar C, Patel K, D'Ancona G, Kent BD, Nesbitt A, Selsick H, et al. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. J Sleep Res. 2018;27(4):e12627.

39. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3):359-370.

40. Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. Hum Psychopharmacol. 2004;19(3):151-180.

41. Mignot EJ. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. Neurotherapeutics. 2012;9(4):739-752.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Thursday 7 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Honoraria for educational activities from Lincoln pharma (May 2019 and September 2018)

Questions for engagement

Issue 1: Treatment pathway	
• Is modafinil the standard first line treatment for excessive sleepiness caused by narcolepsy? • Please outline the current treatment pathway for treating excessive sleepiness caused by narcolepsy. • Should additional lines of treatment be modelled (the analysis currently only models 1 line of treatment after modafinil)? • Does the treatment pathway differ for narcolepsy with cataplexy compared to narcolepsy without cataplexy?	• Yes, modafinil is standard first line treatment. • Current treatment pathway 1. Modafinil and if that fails 2. Dexamphetamine or Methylphenidate and if that fails 3. Sodium Oxybate or Pitolisant (will depend on local availability as well as patient characteristics) • Yes, suggest including Dexamphetamine and/or Methylphenidate in models • It might do depending on the severity of each of the symptoms
• Where in the treatment pathway is solriamfetol likely to be used? What factors influence this decision?	3rd or 4th line. This will be influenced by patient characteristics including co-morbidities (such as OSA, hypertension, cardiac problems) and narcolepsy symptoms (disrupted sleep, cataplexy etc).
• Is prior modafinil a likely treatment effect modifier for treatments given after modafinil (if yes, is this effect the same for all treatments given after modafinil)? Are other prior treatments likely to be treatment effect modifiers?	If a patient has not responded to Modafinil, there is a higher risk they may not respond to other stimulants either. I assume this effect will be similar for all other drugs tried after modafinil but have not seen any data on that. However, the more drugs someone has failed previously, the higher the risk they will not respond to the next drug tried either.

• Are there other factors which are likely treatment effect modifiers (such as cataplexy and containment medications) and what impact could these have on results?	Some patients with cataplexy may have more severe symptoms and be more difficult to treat but again, this is a clinical observation and I cannot recall having seen any published data on this.
Issue 2: Comparators	
• How often are dexamfetamine and methylphenidate used after modafinil in clinical practice? How effective are these treatments for treating excessive daytime sleepiness caused by narcolepsy? Should these treatments be included in base case analysis rather than scenario analysis? • What factors influence the choice of treatments used (for example, does the presence of cataplexy impact treatment choices?).	Please see comments above. Dexamphetamine and methylphenidate commonly used after modafinil. Efficacy varies. Not aware of any recent studies with direct comparisons of these drugs with Modafinil. It seems sensible that these treatments are also included in the analyses. As outlines above, co-morbidities and presence of cataplexy can influence treatment choice.
Issue 3: Generalisability of the clinical trial evidence	
• How generalisable are the results from the TONES trials (particularly TONES 2) to the population seen in clinical practice?	It is a bit strange that not 100% of patients had used stimulants and only about 50% had used Modafinil previously but this may be due to inclusion of patients from countries where sodium oxybate is more readily accessible and Modafinil less accessible than in the UK. The proportion of patients with cataplexy (around 50%) is a bit lower than seen in clinical practice. Severity of sleepiness probably similar or only slightly lower than that seen.
Issue 4: Indirect treatment comparison	

• How robust is the indirect treatment comparison (NMA analysis)? • How uncertain are the comparisons between solriamfetol and the comparator treatments? • Do the results of the indirect treatment comparison, which estimates similar treatment effects (ESS score reduction), for solriamfetol, pitolisant and sodium oxybate, show face validity?	This is extremely difficult to answer. As there are no studies doing a direct comparison of the different drugs, these types of comparisons are the only ones available. This is similar to for example antiepileptic drugs where there are in general also no direct comparisons between treatments. The studies show that the treatment using each of these drugs can be effective but it is not possible to say one is better than the other and I guess that is not what the company is trying to say either or the scope of the engagement to disentangle.
• Do the ERG additions to the NMA make the indirect treatment analysis more robust? Is a random-effects model or fixed effect model more appropriate to use?	I do not have a preference for the comparisons.
Issue 5: Subgroup analysis	
• How robust is the subgroup analysis of people who have had previous modafinil? Is this analysis more appropriate to use to inform the cost-effectiveness estimates? • Would a subgroup analysis for people with and without cataplexy be appropriate? Do some of the treatments available treat cataplexy symptoms also?	Looking at the data for the clarification question d (figures 1 and 2), seems the response is similar for patients who have and have not used Modafinil previously even if ESS absolute numbers are a bit different (table 1). Subgroup analyses of patients with cataplexy might also be useful. Sodium Oxybate does treat cataplexy, pitolisant may have a small effect on cataplexy and occasionally dexamphetamine may provide some improvement of cataplexy but marginal.
Issue 6: Estimation of the treatment effect	

• Is the approach of using only ESS changes from baseline appropriate? Are there any other clinical outcomes which can be used to compare treatment effects?	Although ESS is not the most reliable tool to assess sleepiness, it is commonly used and has been used for a number of years in previous studies and is the only tool available for this type of "historical comparisons". Number of cataplexy attacks and Clinical Global Impression of Change can also be used but the latter may also be subject to bias and is also less easy to compare between centres/clinicians and studies. Clinically, you would look at the "whole picture" including QoL, can the person now work, drive, go out with friends, watch a film from start to finish, but very difficult to use these matters for comparisons in trials/research.
• What is the most appropriate ESS reduction change threshold to use in the analysis to define a response to treatment (reduction of 2 or more, 3 or more, 4 or more, or another threshold)?	3 is usually used. It has not been established what reduction of ESS is clinically relevant and this may also vary from one person to another.
• Is the assumption of a constant treatment effect (maintained reduction in ESS from baseline) for those whose condition responds to treatment appropriate? Is it appropriate to assume the same distribution of response (ESS reduction) across all treatments?	Currently it is not clear if the treatment effect will be constant and maintained. As it is not clear that there will be any reduction in response over time it seems reasonable to assume maintained efficacy in the calculations. It is possible that some patients will respond better than others, i.e. have a greater reduction in ESS. It is likely that will be the case for all the different treatments.
• Is the 8-week timepoint appropriate to capture reduction in ESS treatment effects in the NMA? Does this timepoint underestimate the likely treatment effect of sodium oxybate? If so, is this underestimation likely to be significant?	8-12 weeks would be normal time point to assess efficacy of treatment. Using 8 weeks might potentially underestimate effect of sodium oxybate but unlikely to an extent to render comparisons invalid.
Issue 7: Dosing split	
• What are the most appropriate assumptions relating to the proportion of people on specific doses of each treatment in the	It is likely that if there is a response to treatment at the lower dose, the patient will go on to try the higher dose to see if this might give an even better response if tolerated. I do not think anyone will know how many will be on the higher dose until the drug has been in use for some time. Possibly

analysis (solriamfetol, pitolisant, sodium oxybate, dexamfetamine and methylphenidate)?	75% but that really is a guestimate. It is possible that the split into a larger proportion being on a higher dose than lower would be the same for all the different drugs used and it seems unlikely that one of the drugs would necessarily have a higher proportion in the high dose group than the others.
• How frequently do people change doses or treatments? What factors influence this?	There is no fixed frequency for this as this will depend on treatment response, side effect but also personal preferences as some patients prefer to increase slower if they have had side effects on other drugs or if they have other co-morbidities or are on other drugs.
Issue 8: Treatment discontinuation	
• Are the simplifying assumptions in the model appropriate, including the assumptions that treatment discontinuation rates (resulting from a lack of response or treatment emergent adverse events) are the same for all treatments and that ESS score reductions are constant for people whose disease responses to treatments?	Some patients will discontinue faster than others, particularly if they have adverse events. That will be the same for all treatment options. If by constant ESS reduction in responders you mean if there is evidence for development of tolerance, then yes, some patients do develop a tolerance to Modafinil, dexamphetamine and methylphenidate over time. This is very variable and for some, this happens within a few months whereas for others it hardly seems to happen at all and therefore unpredictable.
Issue 9: Resource use	
• How appropriate is the ERG's assumptions around healthcare resource use, including differing resource use based on whether a person's condition responds to treatment or not? • How valid are the ERG's inclusion and estimation of costs relating to serious adverse events of treatments? Does the	In clinical practice the number of appointments in clinic do not change depending on response as there are usually no free slots available in clinic. But patients who are not doing well may require more frequent phone input that is usually not reimbursed in the same way. Patients with poorly controlled narcolepsy may need increased healthcare input from other resources than the sleep clinic but there is currently limited data on this even if it has been shown in other countries that healthcare use is higher for people with narcolepsy even before diagnosis. Difficult to know. Normally people are not admitted to hospital for treatment adjustments or adverse events. I do not think that differs between treatments. As mentioned above, people with

frequency of serious adverse events of treatment differ by treatment?	poorly controlled narcolepsy may need more healthcare (or have more accidents due to sleepiness) but not necessarily due to adverse events.

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the

NIHR Evidence Synthesis Programme on behalf of NICE

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

Evidence Review Group's comments on the company's response to the technical report

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Irina Tikhonova, David A. Scott, Lorna Hazell, Jonathan Shepherd, Joanne Lord, Joanna Picot

Correspondence to Joanna Picot

Date completed **18 January 2021**

Introduction

This document is the ERG's critique of the response by the company (Jazz Pharmaceutical UK Ltd) to the draft technical report for technical engagement issued by NICE to stakeholders on 7 January 2021. The ERG received the company's response on 8 January 2021.

The company has responded to each of the issues for technical engagement and provided additional cost-effectiveness analyses to address some of the issues.

In this report we present the following:

- ERG critique of the company's response to each of the issues for technical engagement (Issue 1 to Issue 9).
- Validation of cost-effectiveness results presented in the company's response document, including a revised base case and scenarios (Appendix 1).
- Additional ERG analysis to explore a wider range of scenarios (Appendix 2).

Issue 1 – Treatment pathway

Question	ERG comments
Is modafinil the standard first line treatment for excessive sleepiness caused by narcolepsy? Please outline the current treatment pathway for treating excessive sleepiness caused by narcolepsy.	The company argues that modafinil is the standard first-line treatment. This view is supported in the Association of British Neurologists (ABN) submission and response to technical engagement (TE), as well as local treatment pathways cited in the company submission (CS) and opinion from clinical experts consulted by the company and the ERG. The sequencing of other treatments is less clear cut. The ABN TE response states that dexamphetamine or methylphenidate are used after modafinil, followed by sodium oxybate or pitolisant (depending on local availability). However, clinical experts consulted by the company and ERG have suggested that sodium oxybate or pitolisant may sometimes be used at second line. We therefore agree with the company that there appears to be variation in current practice beyond first line treatment.
Should additional lines of treatment be modelled (the analysis currently only models 1 line of treatment after modafinil)?	Further modelling to establish the cost-effectiveness of alternative treatment sequences is challenging because of a lack of clinical evidence. Firstly, effectiveness evidence is very limited for dexamphetamine and methylphenidate (see Issue 2 below). The potential for further modelling of treatment sequencing is also limited by the paucity of evidence on 'degradation' of treatment effects: whether and how effectiveness changes between successive lines of treatment or depending on which drugs have been previously tried and discontinued. In the absence of such information, further modelling by line of treatment would not change current estimates of costs and QALYs.
Does the treatment pathway differ for narcolepsy with cataplexy compared to	The ABN state that the treatment pathway may differ for patients with cataplexy, depending on the severity of symptoms. But in their TE response, the company argues that excessive daytime sleepiness (EDS) is the primary symptom

narcolepsy without cataplexy?	of narcolepsy and that the presence of cataplexy does not impact on the treatment pathway for managing EDS.
Where in the treatment pathway is solriamfetol likely to be used? What factors influence this decision?	There is a difference of opinion on this question. The ABN suggests that solriamfetol is likely to be used at third or fourth line, after modafinil and dexamphetamine and/or methylphenidate. They state that this decision will be influenced by patient characteristics including co-morbidities and narcolepsy symptoms. The company state that solriamfetol is likely to be used at second line, after modafinil. They argue that dexamphetamine and methylphenidate lack evidence of efficacy and have the potential for addiction and abuse. They highlight the unlicensed status of methylphenidate and extended-release dexamphetamine for this indication, noting MHRA guidance that unlicensed products should not be used when a UK-licensed alternative is available. In addition, the company argue that solriamfetol is more convenient for patients than comparators. We note that cost and cost-effectiveness should and will also be considerations. Methylphenidate and dexamphetamine are much less expensive than other comparators, and in practice clinicians report difficulty in accessing more expensive treatments, particularly sodium oxybate.
Is prior modafinil a likely treatment effect modifier for treatments given after modafinil (if yes, is this effect the same for all treatments given after modafinil)? Are other prior treatments likely to be treatment effect modifiers?	We agree with the Company's view that prior modafinil is unlikely to affect the effectiveness of subsequent treatments in a pharmacological sense. However, the Company do not comment on the possibility that some patients might be more resistant to treatment than others. The ABN's TE response does note that if a patient has not responded to modafinil there is a higher risk that they may not respond to their subsequent treatment. The clinical experts consulted by us provided different estimates of the proportion of patients who find modafinil to be ineffective, these estimates range from 10-55% (the CS estimates 20-66%). See Issue 5 below for discussion

	of the TONES 2 subgroup analysis and cost-effectiveness modelling for patients with/without prior modafinil. Any 'other prior treatment' would depend on the treatment sequence, which is also under debate. We are not aware of any evidence that the comparator treatments would be treatment effect modifiers.
Are there other factors which are likely treatment effect modifiers (such as cataplexy and containment medications) and what impact could these have on results?	In the company's response to clarification question A7, they argued that cataplexy is a potential treatment effect modifier, hence its inclusion as a stratification factor and pre-defined subgroup in the TONES 2 trial (see ERG report section 3.3.4). However, results of the TONES 2 subgroup analysis did not show clear evidence of a difference in response for patients with/without cataplexy (ERG report 3.2.5.3). Concomitant medication was also postulated to be a treatment effect modifier based on opinions sought by the company. The company explored the impact of concomitant therapy in an ITC scenario analysis for sodium oxybate (CS B.2.9.2.5) but, with only one sodium oxybate trial that did not include concomitant therapies, it was not possible to determine the true impact of concomitant therapy.

Issue 2 – Comparators

Question	**ERG comments**
How often are dexamfetamine and methylphenidate used after modafinil in clinical practice? How effective are these treatments for treating excessive daytime	The prior use of comparator treatments by patients in TONES 2 is known (CS Table 8), and this shows about [redacted]% of trial participants, in the trial arms relevant to this appraisal, received modafinil. However, we do not know which treatments were received after modafinil. Both clinical experts consulted by the ERG agreed with the company's statement that dexamfetamine and methylphenidate comprise 17.4% and 2.7% of the narcolepsy market, respectively. The CS includes scenario analyses for the comparison with dexamphetamine and methylphenidate. These test a range of

sleepiness caused by narcolepsy? Should these treatments be included in base case analysis rather than scenario analysis? What factors influence the choice of treatments used (for example, does the presence of cataplexy impact treatment choices?).	hypothetical effects on ESS, relative to solriamfetol (CS Tables 74 to 84 and ERG Table 42). These analyses suggest that, due to their low cost, dexamphetamine and methylphenidate may be cost-effective alternatives to solriamfetol. We present further ERG exploratory analysis in Appendix 2 below (section 2.3). This suggests that ICERs for solriamfetol compared with methylphenidate and dexamphetamine exceed £30,000 per QALY gained even when these comparators are assumed to be no more effective than placebo (using estimates of relative effect on 8-week ESS for placebo versus solriamfetol 150 mg from the ERG ITC). However, we acknowledge uncertainty over these results due to the lack of data on adverse effect profiles of dexamphetamine and methylphenidate, and potential loss of effect due to the development of tolerance (TE response Appendix 1.1). The ERG and company exploratory analyses for the comparisons with dexamphetamine and methylphenidate assume equal safety outcomes for all drugs.

Issue 3 – Generalisability of the clinical trial evidence

Question	**ERG comments**
How generalisable are the results from the TONES trials (particularly TONES 2) to the population seen in clinical practice?	The clinicians consulted by the ERG believed that the TONES 2 trial population were reasonably typical of the established population of patients with narcolepsy. They noted that most new cases present in the teenage years or early 20s. The ERG notes that the proportion of people with cataplexy & narcolepsy was about 50% in the Tones 2 trial, and about a third in Tones 1. This is lower than the company estimate of 70%, the ERG clinical expert estimates (50-87.5%) and the evidence from the Narcolepsy UK (NUK) Survey (Appendix 3 of NUK TE response) in which 88% of respondents had Type 1 narcolepsy (i.e. with cataplexy). However, as noted above (Issue 1), although cataplexy has been identified as a potential treatment modifier, the results of the TONES 2 subgroup

	analysis have not shown clear evidence of a difference in response for patients with/without cataplexy. Therefore, the generalisability of the TONES 2 trial results to the population seen in clinical practice may not be affected by differences in the proportions with cataplexy.

Issue 4 – Indirect treatment comparison (ITC)

Question	**ERG comments**
How robust is the indirect treatment comparison (NMA analysis)? How uncertain are the comparisons between solriamfetol and the comparator treatments? Do the results of the indirect treatment comparison, which estimates similar treatment effects (ESS score reduction), for solriamfetol, pitolisant and sodium oxybate, show face validity?	The threshold analyses in CS Table 55 and Table 56 are based on mean differences in 8-week ESS estimated in the company's original ITC analysis with fixed effects (CS Tables 25 and 41). This has much narrower credible intervals than the ERG's revised ITC with random effects (ERG Table 20). The latter gives a much wider range of cost-effectiveness estimates. At the upper limits of the credible intervals for relative effects, pitolisant and sodium oxybate are more effective than solriamfetol, resulting in high ICERs for solriamfetol: £121,409 and £212,077 compared with pitolisant and sodium oxybate respectively in the company's revised base case. Consequently, we cannot agree that the model results are robust to uncertainty in the ERG random effects ITC, which the company accept in their revised base case. We also note that the model does not include correlated values for parameters estimated from the ITC. This means that uncertainty from ITC is poorly characterised in the company's probabilistic sensitivity analysis.
Do the ERG additions to the NMA make the indirect treatment analysis more robust? Is a random-effects model or fixed effect model	We note that the company has included the ERG preferred ITC for relative treatment effects (ERG Table 20) in their revised cost-effectiveness base case. We agree with this, and with the use of the random effects model. See section 1.1 in Appendix 1 below for our replication of the company's revised base case. We agree that use of the random effects, rather than fixed effects model, has little impact on the central cost-

more appropriate to use?	effectiveness results. But, as noted above, the random effects ITC has wider credible intervals, which increases uncertainty over the cost-effectiveness results.

Issue 5 – Subgroup analysis

Question	ERG comments
How robust is the subgroup analysis of people who have had previous modafinil? Is this analysis more appropriate to use to inform the cost-effectiveness estimates? Would a subgroup analysis for people with and without cataplexy be appropriate? Do some of the treatments available treat cataplexy symptoms also?	As stated in our ERG report, the results of the subgroup analysis for people who have had previous modafinil are uncertain because they are based on data from a small number of patients. We agree with the company that this analysis is not powered to assess any difference in efficacy between patients who have had prior modafinil and those who have not. We also agree with the company that data for subgroups previously treated with modafinil are not available for the comparator trials and therefore ITC analysis cannot be conducted for these subgroups. The company do not present cost-effectiveness results by prior modafinil exposure, but we report results obtained by the ERG in Table 3 below. As already stated above (Issue 1 and Issue 3), TONES 2 did not provide evidence of a difference in response for participants with and without cataplexy. Nevertheless, the company report results from the economic model for people with or without the symptoms of cataplexy (Tables 1 and 2 of the company's TE response). The ERG has not been able to replicate these results because we do not have the necessary patient-level data set. The Summaries of Product Characteristics (SPCs) for the comparator drugs indicate that some comparators do treat cataplexy symptoms, as well as EDS, but via different mechanisms of action: Sodium oxybate: therapeutic indication is 'treatment of narcolepsy with cataplexy in adult patients, adolescents and children from the age of 7 years'. Sodium oxybate is a

	sedative, it is believed to act by consolidating night-time sleep and thus improving symptoms. Pitolisant: therapeutic indication is 'treatment of narcolepsy with or without cataplexy' in adults. It enhances the activity of particular neurons in the brain that are part of a major arousal system to promote wakefulness. For dexamphetamine, narcolepsy is mentioned as one of the therapeutic indications but the SPC does not provide any further detail (i.e. whether narcolepsy type 1 or type 2) and cataplexy is not mentioned. For methylphenidate, narcolepsy is not listed as a therapeutic indication (only ADHD).

Issue 6 – Estimation of the treatment effect

Question	**ERG comments**
Is the approach of using only ESS changes from baseline appropriate? Are there any other clinical outcomes which can be used to compare treatment effects?	The clinical experts advising the ERG stated that they do use Epworth scores compared with baseline values as part of their judgement of treatment success, but emphasised that patients' self-reported function and quality of life are also important and considered to come to an overall judgement. They indicated that the MWT is seldom used in clinical practice.
What is the most appropriate ESS reduction change threshold to use in the analysis to define a response to treatment (reduction of 2 or more, 3 or more, 4 or more, or another threshold)?	As noted by the company, there is variation in the literature over the ESS threshold, and clinicians advise that in practice the judgement of what constitutes a response will differ between patients, taking account of other factors as well as change in ESS. Scenario analysis shows that relative cost-effectiveness does not differ when thresholds of 2, 3 or 4 points are used (see Table 4 in the Appendix below). A less stringent ESS threshold (reduction of 2 or more points) results in higher

	estimates of cost and QALY gain for all comparators than does a more stringent threshold (reduction of 4 or more points), but solriamfetol remains dominant or cost-effective in comparison to pitolisant and sodium oxybate.
Is the assumption of a constant treatment effect (maintained reduction in ESS from baseline) for those whose condition responds to treatment appropriate? Is it appropriate to assume the same distribution of response (ESS reduction) across all treatments?	In the absence of evidence or clinical opinion regarding waning of effects for responders over time or differing distributions of response across treatments, we consider it reasonable to assume constant effects and consistent distribution between treatments in the model. Due to the assumption of constant effects, cost-effectiveness results are not sensitive to the time horizon (see Table 4 below). These results will be robust in the presence of waning, provided that treatment is stopped soon after individuals report loss of response.
Is the 8-week timepoint appropriate to capture reduction in ESS treatment effects in the NMA? Does this timepoint underestimate the likely treatment effect of sodium oxybate? If so, is this underestimation likely to be significant?	The ERG agrees with the company that 8 weeks is the longest time point at which data are available for all comparators in the NMA. Clinical advice to the ERG was that it can take at least 3 months of treatment with sodium oxybate before an improvement is seen (partly due to the time taken for dose titration). The degree to which this might cause the treatment effect of sodium oxybate to be underestimated is unclear. The ERG notes that the ABN TE response states that any underestimation is unlikely to be to such an extent that comparisons are invalid. Cost-effectiveness results are not sensitive to the timing of response assessment. With assessment at 12 weeks, solriamfetol is estimated to dominate pitolisant and sodium oxybate (Table 4 below).

Issue 7 – Dosing split

Question	ERG comments
What are the most appropriate assumptions relating to the proportion of people on specific doses of each treatment in the analysis (solriamfetol, pitolisant, sodium oxybate, dexamfetamine and methylphenidate)?	The company report new prescribing data from France and Germany on the proportions of patients who take the 75 mg and the 150 mg doses of solriamfetol (TE section 1.2). These new data are helpful to inform estimates of likely practice in England. The company use the French data in their revised base case (TE response Table 4), although they do not explain why they chose this rather than the German data or a weighted average, and they do not give any information about the numbers of patients on which these proportions are based. Assumptions over the proportion of patients on 75 mg and 150 mg solriamfetol do not change conclusions on cost-effectiveness (Table 4 below). Even with a very high proportion (90%) on the lower dose, although estimated costs and QALYs for solriamfetol are lower than in the base case, the ICER for pitolisant compared with solriamfetol is still very high (over £300,000 per QALY gained) and sodium oxybate is still dominated. The ERG ran scenario analyses to investigate the impact of different sodium oxybate and pitolisant dose splits (ERG report section 5.4.2) because the company did not present these scenario analyses in the CS. Cost-effectiveness results were not sensitive to these changes.
How frequently do people change doses or treatments? What factors influence this?	The ERG is unable to comment on this clinical question.

Issue 8 – Treatment discontinuation

Question	ERG comments
Are the simplifying assumptions in the model appropriate, including the assumptions that treatment discontinuation rates (resulting from a lack of response or treatment emergent adverse events) are the same for all treatments and that ESS score reductions are constant for people whose disease responses to treatments?	The company updated their discontinuation due to TEAEs NMA to include the Harmony Ibis and the Dauvilliers (2013) trials (company TE response, Table 6). It should be noted the ERG analysis includes the latter but not the former (ERG report, Appendix 6). The updated company results follow a similar trend to the analysis presented in the CS (CS Appendix D, Table 46). Notably there is a high level of uncertainty and no statistically significant difference in discontinuation due to TEAEs between solriamfetol 150 mg and comparators. Results in company TE response Table 6 are now presented as odds ratios (solriamfetol 150mg vs comparator) and absolute effects, previously they were presented as risk differences and absolute treatment effects. The updated results are generally in line with the ERG analyses (ERG report, Table 21). The ERG results, from our preferred random effects analysis, are reproduced here as odds ratios and presented versus placebo for ease of interpretation (Figure 1). The ERG also prefers a frequentist approach (MetaInsight) when data are sparse and there and numerous zero events, as previously noted (ERG report section 3.6.3). We can see that only treatment with sodium oxybate 9g leads to a statistically significantly increase in discontinuations due to TEAEs relative to placebo (which aligns with outcomes from the Black 2006 and Xyrem 2005 studies).

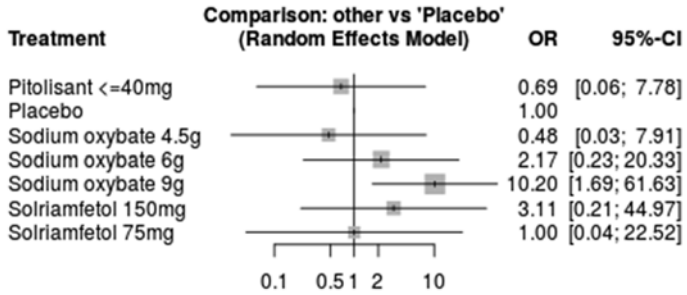


Figure 1 Forest plot of discontinuations due to TEAEs, random effects

However, the lack of data, and events in particular, has led to considerable uncertainty in the results which undermines their reliability. Furthermore, the means and medians (as can be seen from the company analysis) are very different. This reflects a skewed distribution of the data, in which case, using the median value may be more appropriate.

Given the high degree of uncertainty in these results, we do not recommend using them in the base case analysis and support the company's assumption of a similar discontinuation profile across treatments. Nevertheless, it is reassuring that the cost-effectiveness results do not change in the company's scenario analyses with TEAE discontinuation rates from their updated NMA (Table 2 below).

Issue 9 – Resource use

Question	ERG comments
How appropriate is the ERG's assumptions around healthcare resource use, including differing resource use based on whether	Clinical advice to the ERG was that follow-up care may differ for patients with more or less well-controlled symptoms. We therefore consider that the ERG assumptions on additional costs of appointments for responders and for non-responders are appropriate.

a person's condition responds to treatment or not? How valid are the ERG's inclusion and estimation of costs relating to serious adverse events of treatments? Does the frequency of serious adverse events of treatment differ by treatment?	We accept that data on the incidence of serious adverse events is sparse. Nevertheless, we consider it an appropriate conservative assumption to include costs for additional hospitalisations for solriamfetol. Note that these resource assumptions have a negligible effect on modelled costs and cost-effectiveness (see Table 5 below).

Appendix 1 ERG check of company analyses

The company present results for their original and revised base case analyses in Tables 3 and 4, respectively, of their TE response. These results are based on a bootstrap method, with a large number of random resamples from the TONES 2 individual patient data (IPD). The ERG considers that the main results of the model should be based on direct estimates from the original IPD dataset, not from a mean of bootstrapped resamples. 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 (see ERG report section 4.2.6.1). We therefore present all ERG results below using deterministic analysis based on raw IPD. In all cases, our results were very similar to those presented in the company's TE response.

1.1 Revised company base case

Direct (non-bootstrapped) deterministic results for the company's original base case are reported in Table 50 of the CS, reproduced in the top section of Table 1 below. These indicate that pitolisant is more costly and more effective than solriamfetol but with a very high ICER, and that sodium oxybate is dominated by solriamfetol and by pitolisant.

The company introduces two changes to their base case in response to technical engagement.

- First, they use new prescribing data from France to estimate the proportions of patients who use the 75 mg and 150 mg doses of solriamfetol (Issue 7 above).
- Second, they adopt the ERG's effectiveness ITC, which includes additional data from the Harmony Ibis and Dauvilliers trials and an assumption of random effects (Issue 4 above).

We summarise the impact of these two changes in Table 1 below. The new dosing assumption has little impact on cost-effectiveness. But the ERG effectiveness ITC increases the ICER for pitolisant compared with solriamfetol. Overall, these revisions strengthen the company's conclusions from their original base case.

Table 1 Revisions to the company's base case (deterministic with raw IPD)

Scenario	Drug	Total costs (£)	Total QALYs	ICER, fully incremental (£/QALY)	Pairwise CER, Sol versus comparator
Original company base case	Solriamfetol	£8,370	13.369	Reference	Reference
	Pitolisant	£20,991	13.403	£367,368	£367,368 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
French dosing data: solriamfetol [redacted] at 75mg and [redacted] at 150mg	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£20,991	13.403	£361,626	£361,626 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
ERG ITC (random effects with additional Harmony Ibis and Dauvillers data)	Solriamfetol	£8,370	13.369	Reference	Reference
	Pitolisant	£19,242	13.377	£1,390,253	£1,390,253 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Revised base case (with French dosing data and ERG ITC)	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£19,242	13.377	£1,284,981	£1,284,981 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant

Source: CS Table 51 and ERG calculations from model

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

1.2 Company scenario analysis

The company reports other selected changes to their revised base case in Tables 5 and 8 to 14 of their TE response. The ERG reproduced these analyses without bootstrapping (see Table 2 below). For all scenarios, our results are very similar to the company's reported results (with bootstrapping), and consistent with their conclusion that solriamfetol appears cost-effective compared with pitolisant and sodium oxybate.

Table 2 Company scenario analyses (deterministic with raw IPD)

Scenario	Drug	Total costs (£)	Total QALYs	ICER, fully incremental (£/QALY)	Pairwise CER, Sol versus comparator
Revised base case	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£19,242	13.377	£1,284,981	£1,284,981 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Dose split for solriamfetol					
German data: [redacted] 75 mg and [redacted] 150 mg	Solriamfetol	£7,891	13.362	Reference	Reference
	Pitolisant	£19,242	13.377	£777,495	£777,495 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Annual rates of discontinuation due to TEAEs from ITC					
TEAE discontinuation rates from fixed effects ITC	Solriamfetol	£8,832	13.386	Reference	Reference
	Pitolisant	£18,475	13.366	Dominated	Dominant
	Sodium oxybate	£25,350	13.336	Dominated	Dominant
TEAE discontinuation rates from random effects ITC	Solriamfetol	£7,428	13.345	Reference	Reference
	Sodium oxybate	£21,397	13.303	Dominated	Dominant
	Pitolisant	£21,919	13.412	£215,332	£215,332 [SW]
Comparator discontinuation rates (TEAE and loss of effect)					
Rates from year 2 onwards halved for comparators	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£29,945	13.518	£144,446	£144,446 [SW]
	Sodium oxybate	£40,308	13.454	Dominated	£371,700 [SW]
Rates from year 2 onwards set to zero for comparators	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£68,728	14.029	£91,339	£91,339 [SW]
	Sodium oxybate	£92,660	13.883	Dominated	£163,853 [SW]
Rates from year 2 onwards doubled for comparators	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£11,952	13.280	Dominated	Dominant
	Sodium oxybate	£16,020	13.255	Dominated	Dominant
Solriamfetol discontinuation rates (TEAE and loss of effect)					
Rates from year 2 onwards halved for solriamfetol	Solriamfetol	£12,977	13.505	Reference	Reference
	Pitolisant	£19,242	13.377	Dominated	Dominant
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Rates from year 2 onwards doubled for solriamfetol	Solriamfetol	£5,152	13.275	Reference	Reference
	Pitolisant	£19,242	13.377	£138,908	£138,908 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	£341,204 [SW]

Source: ERG calculations from model

[SW] South West quadrant (solriamfetol less costly and less effective than comparator)

1.3 Company subgroup analysis

The company refer to subgroup analysis for prior exposure to modafinil in response to Issue 5, but do not present the results.

Table 3 below reports results for this subgroup analysis obtained by the ERG (deterministic model without bootstrapping, other assumptions as in the company's revised base case). These support the company's conclusion that cost-effectiveness does not differ substantively for people with or without prior exposure to modafinil. We reiterate the company's warnings that this analysis is based on sparse IPD from TONES 2 only, and that relative effects from the ITC are not adjusted for prior modafinil.

Tables 1 and 2 in the company's TE response report subgroup analysis for people with or without symptoms of cataplexy. These suggest that the company's revised base case results do not differ substantively for these subgroups. The ERG was unable to replicate these analyses, as we do not have access to information about baseline cataplexy status for patients in the TONES 2 patient-level dataset on which the model is based.

Table 3 Subgroup analyses on company base case (deterministic with raw IPD)

Scenario	Drug	Total costs (£)	Total QALYs	ICER, fully incremental (£/QALY)	Pairwise CER, Sol versus comparator
Revised base case	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£19,242	13.377	£1,284,981	£1,284,981 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Previous treatment with modafinil					
Prior modafinil	Solriamfetol	£7,989	13.234	Reference	Reference
	Pitolisant	£17,899	13.236	£5,559,116	£5,559,116 [SW]
	Sodium oxybate	£24,892	13.205	Dominated	Dominant
No prior modafinil	Solriamfetol	£9,270	13.608	Reference	Reference
	Pitolisant	£23,072	13.628	£682,244	£682,244 [SW]
	Sodium oxybate	£28,615	13.570	Dominated	Dominant

Source: ERG calculations from model

[SW] South West quadrant (solriamfetol less costly and less effective than comparator)

Appendix 2 Additional ERG analysis

2.1 ERG scenarios

Table 4 shows results obtained by the ERG for a wider range of scenarios. These show that at current prices and with other data and assumptions as in the company's revised base case, the cost-effectiveness results are robust to the model time horizon, the timing of response assessment and definition of response, the dose split for solriamfetol and alternative assumptions about resource use and costs. In all scenarios, sodium oxybate is dominated by solriamfetol; and pitolisant is either dominated by solriamfetol or has a high ICER in comparison with solriamfetol.

Table 4 ERG scenarios on the revised base case (deterministic with raw IPD)

Scenario	Drug	Total costs (£)	Total QALYs	ICER, fully incremental (£/QALY)	Pairwise CER, Sol versus comparator
Revised base case	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£19,242	13.377	£1,284,981	£1,284,981 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Model time horizon (base case 70 years)					
1 year	Solriamfetol	£894	0.323	Reference	Reference
	Pitolisant	£2,162	0.324	£1,374,608	£1,374,608 [SW]
	Sodium oxybate	£2,805	0.320	Dominated	Dominant
5 years	Solriamfetol	£4,949	2.643	Reference	Reference
	Pitolisant	£11,486	2.648	£1,292,407	£1,292,407 [SW]
	Sodium oxybate	£15,391	2.624	Dominated	Dominant
Timing of response assessment (base case 8 weeks)					
Response assessment: time point 12 weeks	Solriamfetol	£8,003	13.366	Reference	Reference
	Pitolisant	£15,292	13.332	Dominated	Dominant
	Sodium oxybate	£21,061	13.302	Dominated	Dominant
Definition of response (base case ESS reduction ≥3 points)					
Definition of response: reduction in ESS≥2 points	Solriamfetol	£9,496	13.397	Reference	Reference
	Pitolisant	£20,991	13.396	Dominated	Dominant
	Sodium oxybate	£30,396	13.366	Dominated	Dominant
Definition of response: reduction in ESS≥4 points	Solriamfetol	£7,114	13.334	Reference	Reference
	Pitolisant	£16,328	13.343	£1,070,764	£1,070,764 [SW]
	Sodium oxybate	£22,138	13.307	Dominated	Dominant

Scenario	Drug	Total costs (£)	Total QALYs	ICER, fully incremental (£/QALY)	Pairwise CER, Sol versus comparator
Dose split for solriamfetol (base case [redacted] 75 mg & [redacted] 150 mg)					
10% 75 mg & 90% 150 mg (ERG base case)	Solriamfetol	£10,287	13.396	Reference	Reference
	Pitolisant	£19,242	13.377	Dominated	Dominant
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
25% 75 mg & 75% 150 mg (ABN estimate)	Solriamfetol	£9,568	13.386	Reference	Reference
	Pitolisant	£19,242	13.377	Dominated	Dominant
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
90% 75 mg & 10% 150 mg	Solriamfetol	£6,453	13.342	Reference	Reference
	Pitolisant	£19,242	13.377	£366,041	£366,041 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Resource use and costs (base case no cost for medical appointments or adverse events)					
Medical appointments for non-responders 4 per year	Solriamfetol	£18,000	13.368	Reference	Reference
	Pitolisant	£28,867	13.377	£1,278,745	£1,278,745 [SW]
	Sodium oxybate	£35,747	13.336	Dominated	Dominant
Medical appointments for non-responders every 6 weeks	Solriamfetol	£29,291	13.368	Reference	Reference
	Pitolisant	£40,096	13.377	£1,271,469	£1,271,469 [SW]
	Sodium oxybate	£47,282	13.336	Dominated	Dominant
Medical appointments for responders as in ERG Table 30	Solriamfetol	£9,122	13.368	Reference	Reference
	Pitolisant	£19,623	13.377	£1,235,637	£1,235,637 [SW]
	Sodium oxybate	£27,015	13.336	Dominated	Dominant
Cost of hospitalisation for SAEs: mean 3.5 days	Solriamfetol	£8,699	13.368	Reference	Reference
	Pitolisant	£19,422	13.377	£1,261,792	£1,261,792 [SW]
	Sodium oxybate	£26,492	13.336	Dominated	Dominant

Source: ERG calculations from model

ABN the Association of British Neurologists

[SW] South West quadrant (solriamfetol less costly and less effective than comparator)

2.2 ERG preferred assumptions

Cost-effectiveness results for the ERG preferred analysis were reported in Table 41 of the ERG report. For completeness, we show the cumulative effect of applying the ERG preferred assumptions to the company's revised base case in Table 5 below. Our assumption that clinicians would consider an ESS reduction of 2 or more points as a response results in very similar QALY estimates for solriamfetol and pitolisant, so solriamfetol dominates pitolisant. ERG changes to baseline patient characteristics (to reflect the whole population in TONES

2, rather than just those in the 150 mg arm in the company base case) increase QALY estimates but do not change the cost-effectiveness results. Similarly, our changes to assumptions about resource use increase costs across all comparators, but do not change relative cost-effectiveness.

Table 5 Cumulative change to ERG preferred analysis (deterministic with raw IPD)

Scenario	Drug	Total costs (£)	Total QALYs	ICER, fully incremental (£/QALY)	Pairwise CER, Sol versus comparator
Revised base case	Solriamfetol	£8,322	13.368	Reference	Reference
	Pitolisant	£19,242	13.377	£1,284,981	£1,284,981 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Revised company base case (ERG corrected: cost of non-responders)	Solriamfetol	£8,317	13.368	Reference	Reference
	Pitolisant	£19,237	13.377	£1,284,961	£1,284,961 [SW]
	Sodium oxybate	£25,856	13.336	Dominated	Dominant
+ Population: mean age [redacted] years, [redacted] female, mean ESS baseline [redacted]	Solriamfetol	£8,321	13.487	Reference	Reference
	Pitolisant	£19,246	13.495	£1,267,875	£1,267,875 [SW]
	Sodium oxybate	£25,868	13.454	Dominated	Dominant
+ Definition of response, ESS reduction ≥ 2 points	Solriamfetol	£9,495	13.516	Reference	Reference
	Pitolisant	£20,995	13.515	Dominated	Dominant
	Sodium oxybate	£30,405	13.483	Dominated	Dominant
+ Cost of hospitalisation for SAEs: mean 3.5 days	Solriamfetol	£9,924	13.516	Reference	Reference
	Pitolisant	£21,191	13.515	Dominated	Dominant
	Sodium oxybate	£31,187	13.483	Dominated	Dominant
+ Medical appointments for responders as in ERG Table 30	Solriamfetol	£10,839	13.516	Reference	Reference
	Pitolisant	£21,607	13.515	Dominated	Dominant
	Sodium oxybate	£32,600	13.483	Dominated	Dominant
+ Medical appointments for non-responders 4 per year	Solriamfetol	£20,381	13.516	Reference	Reference
	Pitolisant	£31,169	13.515	Dominated	Dominant
	Sodium oxybate	£42,309	13.483	Dominated	Dominant
+ Solriamfetol dose split 10% 75 mg & 90% 150 mg	Solriamfetol	£23,086	13.547	Reference	Reference
	Pitolisant	£31,169	13.515	Dominated	Dominant
	Sodium oxybate	£42,309	13.483	Dominated	Dominant
ERG base case	Solriamfetol	£23,086	13.547	Reference	Reference
	Pitolisant	£31,169	13.515	Dominated	Dominant
	Sodium oxybate	£42,309	13.483	Dominated	Dominant

Source: ERG calculations from model

[SW] South West quadrant (solriamfetol less costly and less effective than comparator)

2.3 Exploratory analysis with other comparators

As we discuss in Issue 1 above, the comparison with dexamphetamine and methylphenidate is hampered by a lack of effectiveness data. In their original submission, the company presented two-way scenario analyses to explore the cost-effectiveness of these additional comparators, with hypothetical assumptions about relative effects and cost (CS Tables 74 to 84). We follow this approach in two further exploratory analyses applied to the company's revised base case, presented in Table 6 below.

These scenarios are intended to test whether solriamfetol might be a cost-effective alternative to methylphenidate and dexamphetamine under optimistic assumptions.
We therefore assume relatively high daily costs for methylphenidate (£1.92; one 40 mg MR capsule) and dexamphetamine (£5.30; two 20 mg tablets) and that their relative effects are no better than placebo. The ERG ITC analysis, accepted in the revised company base case, estimated a mean 8-week reduction in ESS of -3.098 points (95% credible interval -6.907 to 0.707) for placebo compared with 150 mg solriamfetol (ERG report Table 20). We use the mean and lower credible interval estimates in our two scenarios.

The results suggest that solriamfetol is unlikely to be a cost-effective alternative to methylphenidate or dexamfetamine. In the most optimistic scenario, with an ESS reduction of nearly 7 points for solriamfetol compared with dexamfetamine and methylphenidate, the ICERs for solriamfetol still exceed £30,000 per QALY gained. Results are very similar if the IPD data from TONES 2 used in the model is restricted to patients with prior exposure to modafinil. Estimated ICERs for solriamfetol compared with methylphenidate and dexamphetamine are higher when these scenarios are applied to the ERG preferred set of assumptions.

We caution that, although these scenarios are extreme in assuming that methylphenidate and dexamphetamine are no more effective at reducing ESS than placebo, the scenarios assume no difference in safety outcomes between any of the comparators. This might not be realistic.

Table 6 ERG exploratory analysis with methylphenidate and dexamphetamine: company revised base case (deterministic with raw IPD)

Scenario	Drug	Total costs (£)	Total QALYs	ICER, fully incremental (£/QALY)	Pairwise CER, Sol versus comparator
Assumed difference in ESS reduction versus solriamfetol 150 mg [redacted] (mean for placebo)*	Methylphenidate	£899	13.228	Reference	£53,003
	Dexamfetamine	£2,484	13.228	Dominated	£41,689
	Solriamfetol	£8,322	13.368	£53,003	Reference
	Pitolisant	£19,242	13.377	£1,284,981	£1,284,981 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant
Assumed difference in ESS reduction versus solriamfetol 150 mg [redacted] (lower 95% credible interval for placebo)*	Methylphenidate	£314	13.143	Reference	£35,620
	Dexamfetamine	£867	13.143	Dominated	£33,160
	Solriamfetol	£8,322	13.368	£35,620	Reference
	Pitolisant	£19,242	13.377	£1,284,981	£1,284,981 [SW]
	Sodium oxybate	£25,860	13.336	Dominated	Dominant

Source: ERG calculations from model

[SW] South West quadrant (solriamfetol less costly and less effective than comparator)

* See ERG Report Table 20: 8-week ESS, random effects model (ERG base case)